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CONTENTS

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COELIAC DISEASE: A RELATION BETWEEN DIETARY STARCH AND FAT ABSORPTION

BY

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(From the Hospital for Sick Children, Great Ormond Street, and King's College Hospital)

In a previous communication (1948) reasons were given for regarding starch intolerance in children with coeliac disease as perhaps of greater etiological importance than the well known failure to absorb the products of fat digestion. These reasons were (1) coeliac disease usually begins between six months and two or three years of age, and during infancy, at a time when their diet consists of milk, the children who eventually develop this disorder show no indication of what is to come. It is clear that the constituents of milk present no difficulty to the infant who later develops coeliac disease. (2) The principal dietetic change that occurs during the age when coeliac disease becomes manifest consists of a steadily increasing intake of starches. (3) Abdominal distension, which is so constant a characteristic of coeliac children, is not exhibited to any noteworthy degree in infants who for other reasons are intolerant solely of fat, and in coeliac children this feature is much more attributable to fermentation of carbohydrate than to unabsorbed fat.

Assuming that intolerance of starch exerts a primary etiological role in coeliac children, and that failure to absorb fat is a secondary consequence dependent in some way upon mismanagement of starch, it might be possible to improve fat absorption by eliminating starch from the diet, always provided that the failure of fat absorption does not so alter conditions in the intestine that once this failure has developed it then persists by its own mechanism. It was decided to put this matter to trial by feeding coeliac children on two consecutive diets, both containing an ample portion of fat, the first diet containing starch and the second being free of starch, and to compare the absorption of fat from each diet by means of fat balances. It was soon evident that fat absorption was much improved on a diet free from starch. The investigation was then reversed, beginning with a starch-free diet and later changing to one containing starch; again it was demonstrated that the inclusion of starch in the diet lowered the absorption of fat.

Experiments on these lines have been conducted on fifteen children with coeliac disease, and the results, which are set out in table 1, form the basis of this communication.

Clinical Cases

With the possible exception of case 7, all the children fulfilled the requirements for a diagnosis of coeliac disease. Their illness had started between ten months and three years of age, after a healthy infancy. Failure of appetite, irritability, loss of weight, often to a severe degree, abdominal distension, and the passage of loose, pale, offensive motions were the characteristic features. Analyses of the stool fats showed these to range between 40 and 60 per cent. of the dried stool. In every case tuberculin skin tests were negative, and in those submitted to x-ray examination of the chest and abdomen there was no evidence of tuberculous infection. The oral glucose tolerance curve was flat. The duodenal juice of each child was shown to contain trypsin, lipase, and amylase. The stools were examined for parasitic ova and for cysts of Lamblia with negative results. The exception was case 7, in whom after several negative examinations, a stool was found to contain Lamblia cysts. By that time she had completed the first half of her dietetic experiment and, as her other symptoms of wasting (at four and a half years she weighed 26 lb.), abdominal distension, typical motions, and a flat oral glucose curve were so suggestive of coeliac disease, her experiment was allowed to continue. She was given a course of mepacrine, 0·05 g. twice daily for five days, between her two fat balances, and subsequently evidence of Lamblia infection disappeared. It was thought justifiable to include her results in this series, but were her case withheld the conclusions reached on the remainder would not be affected.

Cases 1 to 7 inclusive were new patients hitherto untreated for coeliac disease. Of these, the condition of nos. 1, 3, 4, 6, and 7 could be assessed clinically as severe, nos. 2 and 5 as moderate. Cases 8 to 15 inclusive had undergone previous treatment in various hospitals with varying degrees of improvement. Of these, at the time their experiment began, nos. 8 and 14 were still clinically severe,

TABLE 1
ANALYSIS OF FINDINGS IN EXPERIMENTS WITH STARCH AND STARCH-FREE DIETS

Case no.	Initials	Sex	Age (years)	Duration of illness (years)	Diet with starch						Diet with no starch					Diet with starch						Difference between starch-free diet and starch diet
					Protein (g.)	Fat (g.)	Sugars (g.)	Starch (g.)	No. of days on diet before balance begun	Percentage fat absorption over 12 days	Protein (g.)	Fat (g.)	Sugars (g.)	No. of days on diet before balance begun	Percentage fat absorption over 12 days	Protein (g.)	Fat (g.)	Sugars (g.)	Starch (g.)	No. of days on diet before balance begun	Percentage fat absorption over 12 days	
1	N.W.	M.	4	1½	45	51	96	59	34	51	85	48	195	20	77							+26
2	K.D.	F.	1 1/6	1/3	45	25	98	30	6	69*	86	48	216	4	91*							+22
3	V.C.	F.	5	4	32	45	47	24	10	72	67	56	159	17	89							+17
4	A.G.	M.	3½	1½							86	48	216	28	89	78	40	107	120	8	65	+24
4a	A.G.										86	48	216	210	92	75	39	165	82	16	73	+19
5	R.C.	F.	1 3/3	½	41	24	81	99	9	82	86	48	216	7	99							+17
6	R.J.	M.	3	½	46	46	102	66	9	64*	93	61	212	21	89							+25
7	B.B.	F.	4½	2	48	50	89	78	10	80	87	57	192	21	93							+13
8	J.C.	M.	6½	5							105	65	210	16	85	94	44	135	69	18	61	+24
9	P.R.	F.	4	2½							86	48	201	18	91	74	49	106	80	7	80	+11
10	P.L.	M.	3	1½	48	50	89	78	11	85	87	61	192	18	88							+ 3
11	B.L.	M.	4	2	41	24	81	99	9	59	86	48	216	7	84							+25
12	C.W.	F.	4	2½	57	67	109	7	99	86	108	67	170	9	83							— 3
13	R.E.	M.	6	3							87	58	192	7	87	54	53	90	82	21	83	+ 4
14	P.D.	F.	5	3							106	47	219	30	88	78	40	107	120	7	78	+10
15	J.R.	F.	4	2¾							77	40	201	30	92	78	40	129	45	8	83*	+ 9
	Average									72·0					88·6						74·4	Mean difference +15·4

* Indicates eight-day balance.

nos. 9, 11, 12, and 15 were moderate, and nos. 10 and 13 could be regarded as mild.

Attention must be drawn to cases 4 and 4a. These refer to one and the same child. The first experiment was conducted on his admission. He was then put on a starch-free diet, with considerable benefit, over a period of 210 days, and the experiment was then repeated. It was thought that perhaps after so long a period of improvement, during which he had gained 12 lb. in weight, the addition of starch might not affect his capacity to absorb fat, but this was not so; his fat absorption fell from a normal figure of 92 per cent. to 73 per cent.

In case 10 the fat absorption on a starch-free diet would probably have been higher had he not had an upper respiratory infection during the middle four days of his twelve-day balance. This was the only occasion on which an infection might have vitiated the fat balance results.

The diets. The starch-containing diet conformed roughly to the ordinary ward diet. Tradition dies hard, and the concept of a low-fat diet for coeliac children had been the custom for so long that a word of praise is due to the dietitians who elaborated for these children diets containing unskimmed milk and virtually a normal amount of fat. The total daily intake of milk was for some children reduced to half a pint or less, drinks of milk being replaced by Prosol made with water. Prosol is a powder having a composition of protein 63 per cent., fat 1 per cent., carbohydrate 26 per cent.

One knows by experience how badly coeliac children tolerate a normal diet unmodified in any way, and the question of whether to start the balance experiments on a starch-containing or a starch-free diet was sometimes decided by the inability of the children to tolerate the former diet. In other children who began with a starch-containing diet, their condition steadily deteriorated, and only the skill of the nursing staff in persuading the children to take their food enabled this part of the experiment to continue for the required time. From these remarks it will be correctly gathered that of the two diets the one without starch was the better tolerated. Even after a period of improvement on a starch-free diet, in some children the change to a diet containing starch so interfered with health and appetite that the conduction of a twelve-day balance presented considerable difficulty, and in case 16 the change for the worse was so serious that the second balance had to be abandoned. It was eventually carried out three months later after the child's health had been steadily built up on a starch-free diet.

A starch-free diet would have been difficult to produce in a form acceptable to the children without the use of Soya bean flour. This contains considerably more protein and fat than other flours, but is devoid of starch, the carbohydrate being in the form of dextrins. It has a different taste from other flours, and the children often required a few days to become accustomed to it. A recipe of Soya flour 6 oz., margarine 4 oz., sugar 4 oz., and one egg was used to prepare Soya biscuits, and these not only gave the sense of repletion ordinarily provided by starch, but provided something firm for the children to bite upon in place of bread or toast.

It had originally been hoped that the calorie value of the two diets would be approximately the same, but Soya flour has a higher calorie value than other flours, and this difference is still further enhanced by the recipe for Soya biscuits; consequently the starch-free diet always had a higher calorie content than the diet with starch. For this reason it has been thought necessary to show in table 1 the composition of each child's diets in grammes of protein, fat, sugars (including dextrins), and starch. It will be noted that the starch-free diet contained more protein and sugar and to a less extent more fat than the starch-containing diet.

The daily intake of fat on the starch-free diet averaged 53 g., or 11½ oz. per week, which may be compared with the standard ration in this country for children of two to five years of 12½ oz. per week, calculated to include their pint of milk daily, and their weekly ration of bacon, egg, and cheese.

With regard to the size of the diet, this had to be gauged as closely as possible in relation to each child's appetite, so that while the intake should be enough to satisfy, refusal of food or vomiting should be reduced as much as possible, as of course all such rejections had to be measured. A week was often required after the diet had been changed to adjust the intake to the appetite.

As an example of the actual diets, those given to case 9 are set out in table 2. These have been selected because the starch-free diet contained only 100 calories per day more than the starch-containing diet. The average difference in calories between the two diets was 315 calories.

Technique. Frazer (1947) has stated that a normal human subject on a diet containing 50 g. of fat absorbs 95 per cent. or more of the fat ingested, and that fat absorption may be regarded as defective in all cases absorbing 90 per cent. or less. Fat absorption is known to be defective in tropical sprue, and Black and Fourman (1947), when conducting fat balance investigations in this condition, pointed out that the customary period of four days for a balance test was unreliable because consecutive four-day balances could show considerable variation in the amount of fat absorbed, and they therefore extended the period in their investigations to twelve days. It would seem that in a normal subject a four-day period for a balance test may be sufficiently long, but that when a defect in fat absorption is to be expected a longer period is required. Failure to absorb fat is constantly found in coeliac disease and therefore it was decided to conduct the balances on the coeliac children over twelve-day periods. The procedure adopted was to carry out three consecutive four-day balances, the results being totalled to give a twelve-day balance.

TABLE 2
EXAMPLE OF THE ACTUAL DIETS (CASE 9)

	Starch-containing		Starch-free	
During the day ..	Prosol (1 in 8)	1 pint	Prosol (1 in 8)	1 pint
	Dextri-maltose	1 oz.	Dextri-maltose	1 oz.
	Radiostoleum	10 drops	Radiostoleum	10 drops
	Ascorbic acid	50 mg.	Ascorbic acid	50 mg.
Breakfast	Prosol		Prosol	
	Bread	1 oz.	Banana purée	4 oz.
	Butter	½ oz.	2 Soya biscuits	
	1 egg			
Dinner	Minced chicken	1 oz.	Minced chicken	1 oz.
	Potato	2 oz.	Tomato purée	4 oz.
	Butter	½ oz.	Spinach, beetroot, or cauli-flower purée	2 oz.
	Rice	10 gm.	Milk 5 oz.)	egg
	Milk	5 oz.	½ egg)	custard
	Black currant purée	1 oz.	Sugar 10 g.)	
	Sugar	10 g.	Cooked apple purée	4 oz.
			Honey	½ oz.
Tea	Bread	1 oz.	Prosol	
	Butter	½ oz.	Banana purée	4 oz.
	Wheaten biscuits	½ oz.	2 Soya biscuits	
	Prosol			
Supper	Wheaten biscuits	1 oz.	Prosol	
	Prosol		Egg custard	5 oz.
			Apple purée	4 oz.
			Honey	½ oz.
			2 Soya biscuits	
Calorie value	1,483 C.		1,585 C.	

It has already been pointed out that the condition of the children sometimes made it very difficult, if not impossible, to maintain the balance for as long as twelve days, especially during the phase of the starch-containing diet, and in fact on four occasions the balance had to be discontinued after eight days. The cases in which this occurred are indicated in table 1; apart from them, all the balances in that table refer to a twelve-day period. The performance of balances over such a relatively long period added very considerably to the work of the nursing staff, and made heavy inroads on the working capacity of the laboratories; in fact this latter problem became so serious as to reduce the number of children on whom these investigations could otherwise have been carried out. During the final analysis of results the opportunity has been taken to inquire whether a twelve-day period was really essential and, as will appear later, it would seem that the broad conclusions would have been the same had the period been one of eight days.

The estimation of the total amount of fat in each four-day collection of stools was carried out in the laboratories at Great Ormond Street under the direction of Dr. W. W. Payne, and at King's College Hospital under Professor Gray, and I am deeply indebted to them and their technicians for making this investigation possible. In all cases the estimate of fat was made from the dried stool. Although methods of sampling differed slightly at the two hospitals and at the former carmine was used as a marker, whereas at the latter a high enema was employed for this purpose, the results from the two laboratories were similar. Actually cases 2, 11, and 12 were from King's College Hospital, the remainder from Great Ormond Street and its country branch at Tadworth.

During the period of the balance the daily intake of fat was measured, any food refused or vomited being deducted from the daily intake. The difference between the total intake of fat and the total output in the faeces gave the amount of fat absorbed, and this, expressed as a percentage of the total fat intake, gave the percentage fat absorption.

It was impossible to perform the balances on a strictly consecutive series of cases because no really reliable technique for collecting the whole of the stools from incontinent children could be developed. These children, two or three in number, were therefore not used, but with these exceptions the series was consecutive.

When this investigation began, no information

was available as to the length of time a child should be on a particular diet before the balance was started. It was soon realized that when carmine was used as a marker it appeared in the stools usually within twenty-four hours, and therefore any alteration in the diet ought to be reflected in the stools within two or three days. But even if dietary starch should interfere with fat absorption, the mechanism of this was not understood, and were it to depend upon a modification of the intestinal flora, it was thought that this might take several days to develop. It was also uncertain whether an alteration in the fat absorption caused by a change of diet would become quickly maximal or be progressively greater the longer the diet was continued; were the latter to be true, the longer the interval before the balance was started the more apparent would be any change in fat absorption. In consequence of these difficulties, no fixed interval has been used. When a change in diet gave rise to deterioration in the child's condition, the balance was started after about a week, but in other children three or four weeks were allowed to elapse. Owing to these differences the interval between a new diet and the ensuing balance has been indicated in table 1. The shortest interval occurred in case 2, owing to pressure to have the child home, and it is interesting that after only four days on a starch-free diet a radical improvement in fat absorption was manifest.

The absence of controls from normal children is simply explained. If a normal child absorbs at least 90 per cent., and usually 95 per cent. of ingested fat, it would be impossible to register any considerable rise in fat absorption whether the diet contained starch or was starch-free. By carrying out balances on each child while receiving a starch-containing, and a starch-free, diet, each child became its own control, and this was enhanced by varying the order in which the two diets were taken.

It was felt to be desirable that the results should be submitted to statistical analysis, and for this purpose the four-day balances as well as the twelve-day totalled results were sent to Dr. Fraser Roberts of the London School of Hygiene and Tropical Medicine, to whom I am greatly indebted for his report. He did not receive the results from case 16, as these were not completed at the time. To quote from his report: 'The standard deviation of a four-day estimate of percentage fat absorption during the starch period is 6·15; increasing this to eight days reduces the standard deviation to 4·32; increasing to twelve days reduces it to 3·53. For the starch-free diet the standard deviation for a four-day period is 3·60; for eight days 2·55; for twelve days 2·08. The accuracy of estimate over four days on the starch-free diet is just about equal to the accuracy of estimate over twelve days on the starch diet. This might suggest using twelve- and four-day periods respectively for the two diets; actually, however, almost exactly the same accuracy is obtained by measuring both over eight days.

'With regard to what period you can most profitably use in the future in order to establish a difference of the order shown by the fifteen children with high significance (chance that it could be due to chance 1/100), you would require the following numbers: four-day balance, five children; eight-day balance, four children; twelve-day balance, three-four children (but nearer four than three). To establish that there was such a difference with very high significance (chance that it could be due to chance 1/1,000) you would require: four-day balance, seven children; eight-day balance, five or six children (but nearer six than five); twelve-day balance, five children.

'I hope that these figures will help you to weigh the relative advantages of saving laboratory time and doing the work with fewer children. There may be, of course, physiological reasons why duplicate determinations are desirable, but I should imagine that in any event there is a good case for reducing the period from twelve days to eight.

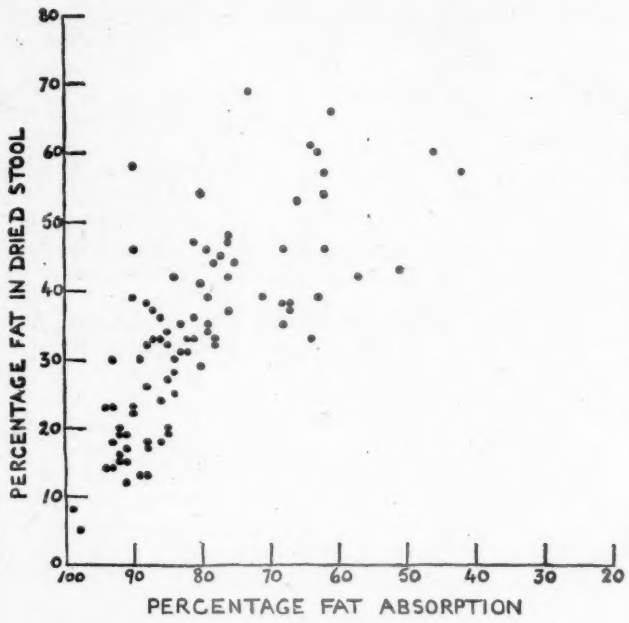
'With regard to the twelve-day balances, the mean difference between the starch-free diet and the starch-containing diet is highly significant and has actually been estimated with fair precision using only fifteen children.'

The greater variation between consecutive four-day balances on a starch-containing diet as compared with a starch-free diet is probably due to the percentage fat absorption on the latter diet more closely approximating to the normal, and not because of any peculiar vice in the starch-containing diet. In other words, the reliability of a single four-day balance becomes greater as the percentage fat absorption moves towards the normal, irrespective of the diet. This is shown in table 3, based on an analysis of the four-day balances.

TABLE 3
ANALYSIS OF THE FOUR-DAY BALANCES

Twelve-day percentage fat absorption	The maximum difference in the groups of three four-day percentage fat absorptions averaged	Number of four-day estimations
Between 90 and 99	3·7	18
Between 80 and 89	5·7	44
Between 70 and 79	12·8	13
Between 50 and 69	10·7	15

An isolated faecal fat estimation is of course a less arduous and much shorter investigation than a fat balance. It is therefore appropriate to enquire whether fat absorption can be gauged with any degree of reliability merely from faecal fat estimations. The present investigation offers material for an answer to this question. The figure shows the percentage fat absorption plotted against the percentage of total fat in the dried stool, the figures being obtained from ninety four-day balances. It can be seen that a rough generalization could be made to the effect that the higher the amount of fat in the stools the lower is the fat absorption likely



to be, but the plotted points are too widely scattered for this statement to be at all reliable in the interpretation of an individual estimate of faecal fat. A good illustration can be gathered from the five cases in which fat absorption was 90 per cent.; the total fat in the dried stools of these cases ranged between 22 per cent. and 58 per cent. As might be expected, and as is often observed in coeliac children, if the dietary fat is sufficiently reduced the percentage of fat in the dried stool can be lowered even to single figures, but there is no evidence to show whether this is accompanied by improvement in the absorption of fat. It must be concluded that in coeliac children an isolated estimation of faecal fat does not give any reliable information of the percentage fat absorption.

Effect of a starch-free diet. A study of the effect of a starch-free diet on the health and well-being of coeliac children was not the primary purpose of the enquiry, but the following observations can be made.

Adaptation to the diet. Children with a difficult appetite and an antipathy to new tastes took up to a week before they were taking the diet with relish; Soya biscuits, although quite palatable, differ in taste from other starchy foods, and some children needed persuasion to try them. Others with a satisfactory appetite went on to the new diet at once and without difficulty. During the period of adaptation only one child lost weight, and that less than a pound.

Weight. On a starch-free diet every child gained weight steadily. The average increase was at the rate of a pound per fortnight; the two most satisfactory gains were 6 lb. in six weeks, and 10 lb. in twelve weeks.

Stools. Prior to the new diet the stools were frequent, loose, and pale. The loose character lasted as a rule about a fortnight, the stools then gradually became formed and remained of this consistency, and their colour became more normal.

Abdominal distension. On the whole this tended to lessen, but not to any great extent, although as the children became plump the distension was less noticeable. On the other hand when a reversion was made to a starchy diet an increase in abdominal distension was soon apparent, and this was accompanied by diminution of appetite, abdominal discomfort, and a very noticeable increase of temperamental irritability.

Temperament. The change for the better in temperament and activity was very striking. Within a few weeks the children were smiling, happy, playful, and actively running about the ward, so much so that one boy practising to be a paratrooper leapt from his bed and unfortunately broke his leg.

Conclusions

1. In a group of fifteen children with coeliac disease the withdrawal of starch from the diet was accompanied by a rise in the fat absorption that averaged 15 per cent.

2. The figure of 15 per cent. in this investigation is of high statistical significance.

3. The starch-free diet enabled the children to tolerate virtually a normal fat intake, and led to improvement in weight, the character of the stools, and temperament.

4. A four-day period for a fat balance is too short when fat absorption is defective. Although a twelve-day period was employed in this investigation, an eight-day period would have been sufficient.

5. Estimations of faecal fat alone do not provide a reliable index of the fat absorption.

In addition to those mentioned in the text, I wish to express my gratitude to the sisters and nursing staff of my ward at The Hospital for Sick Children, Great Ormond Street, the hospital's country branch at Tadworth Court, and King's College Hospital, for their unremitting help and encouragement.

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BLOOD VOLUME STUDIES IN HEALTHY CHILDREN*

BY

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Among the earliest recorded experiments on the estimation of the blood volume are those of Bischoff (1856, 1858) and Welcker (1858), who by exsanguination measured directly the amount of blood obtained from the bodies of executed criminals. Since that time much ingenuity has been exercised in devising methods of estimating blood volume which would combine accuracy with ease of application to the living human subject. The modern techniques involving the use of dyes owe their origin to the work of Keith et al. in 1915, and are in the writer's opinion the most practical of all the methods. These techniques have undergone several modifications, the two most important being the substitution of a blue for a red dye and the adoption of the photoelectric absorptiometer for comparison of colours. The blue dye (Evans blue, or T1824) now in common use, is more slowly excreted than the red dyes, such as vital red and congo red (Dawson et al., 1920), and, what is probably more important, does not mask the occurrence of haemolysis. Indeed the Evans blue method used in these studies not only permits the detection of haemolysis but allows for its correction. The photoelectric absorptiometer eliminates the personal factor involved in colour matching.

Of recent years much information has been gained regarding the changes in the volume of plasma and blood in such states as shock, dehydration, and anaemia. Most of the investigations, however, have been carried out in adults, and comparatively little work has been done in children, where the technical difficulty of venepuncture is greater. It is evident that any study of changes in the blood volume in children and their application to disease must depend on the establishment of a normal range of values. This range will possess wide limits, since the blood volume is constantly changing with growth. It was considered necessary, therefore, as a preliminary procedure, to define the average volumes and the range at various ages as accurately as possible.

The object of this paper is to report the results obtained from the plasma and blood volume studies of eighty apparently healthy children varying in age from three months to thirteen years, forty-two girls and thirty-eight boys, all in-patients of the Royal Hospital for Sick Children, Glasgow. In each instance the investigation was delayed until convalescence was well established and the child ready for dismissal. All the subjects were afebrile and on full diet, and none had diarrhoea or vomiting. The state of nutrition was also considered, and only those between 80 and 110 per cent. of their expected weight chosen (Holt's tables). The haemoglobin level was not less than 10 g. per cent., except in the group of infants, where two babies were included with haemoglobin values of 9·5 g. per cent. The studies have been grouped and averaged according to age; six subjects in each year were investigated (except in the first year, when ten cases were done), and the average recorded at three-monthly periods. For the first twenty-three cases the dye used was congo red, as at that time the advantages possessed by Evans blue were not fully appreciated. The plasma volume of the remaining fifty-seven cases was investigated with Evans blue. There is evidence to show, however, that the results are comparable.

Methods

Preparation of patient. On the morning of the investigation, in accordance with the technique used by most workers, the children were kept in bed and given nothing to eat or drink after 9 a.m. save sips of water. Estimations were carried out about five hours later between 2 and 3 p.m. Immediately before the start of the experiment the weight and height of each child were taken and recorded.

Procedure. For the dye injections a 5-ml. syringe accurately calibrated in fifths of a millilitre was used throughout. By venepuncture, 6 to 8 ml. of blood were removed, and through the same needle the dye solution (whether Evans blue or congo red) was injected. Blood was withdrawn into the syringe and the syringe washed out once. A mixing time of ten minutes was allowed. This interval was chosen after estimations on two of the older children from whom samples of blood were withdrawn every two minutes for twelve minutes and then every ten minutes for half an hour. The results of the dye

* This publication has been adapted from part of a thesis submitted for the degree of M.D. at the University of Glasgow.

concentrations when graphed against time showed a ' mixing curve ' lasting ten minutes as described by Gibson and Evans (1937a) followed by a gradual ' disappearance slope ' (Fig. 1). Thus the mixing time allowed was ten minutes, which is in accordance with the reports of others (Davis, 1942; Gregersen, 1944; Noble and Gregersen, 1946). After this interval 6 to 8 ml. of blood were again withdrawn using a different vein. In each case, after the introduction of the needle into the vein, all constriction was released and a minute allowed to elapse before blood was withdrawn, thus avoiding errors attributable to venous stasis. To prevent haemolysis, the blood was withdrawn into dry syringes and then ejected without frothing down the sides of the receiving tubes. The latter were graduated centrifuge tubes containing 0·3 ml. of an anticoagulant which did not alter the osmotic pressure of the plasma. The mixture used was that advocated by Wintrobe and Landsberg (1935), a solution of 2 per cent. potassium oxalate and 3 per cent. ammonium oxalate. The tubes were then covered with light aluminium caps to prevent evaporation and centrifuged at 2,800 r.p.m. for thirty minutes. The haematocrit readings of the two tubes were taken and averaged, allowance being made for the dilution with the oxalate mixture. The difference in the two readings as a rule was

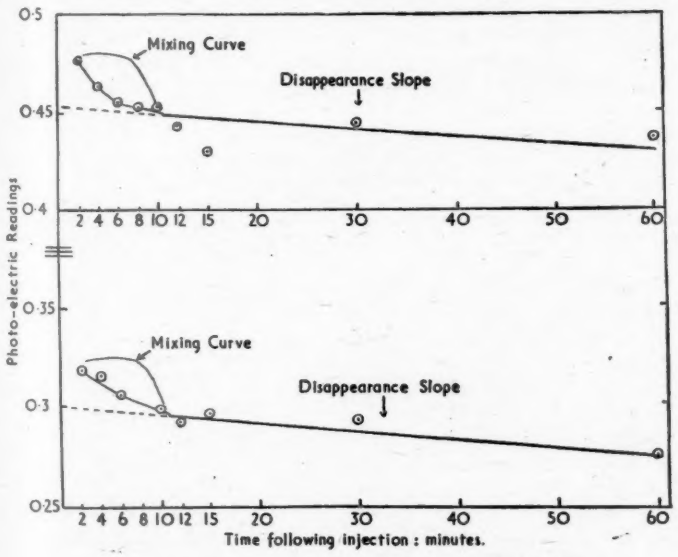

FIG. 1.—Time-excretion graphs for Evans blue.

insignificant. The plasma obtained after centrifuging was pipetted off and used in the cups of the photoelectric apparatus without further preparation, except in the congo red experiments where dilution to 1 in 2 of the specimens of plasma with normal saline was usually required.

The photoelectric technique was similar for both dye methods, apart from the use of different coloured filters which will be discussed later. After ' setting ' the colorimeter, the undyed plasma was placed in the specimen cup and a reading taken, to be followed by a reading for the dyed plasma. In both cases the ' blank ' cup was filled with distilled water. By subtracting the former from the latter result, the colour effect of natural plasma was removed, and the reading due to dye alone obtained. A graph plotted from the readings of the standard dilutions of the dye in use gave the concentration attained by the dye in the plasma. The final calculations were simple.

$$(1)\ \text{P.V.} = \frac{D \times a}{y}$$

where P.V. = plasma volume
D = dilution of dye in the plasma
a = amount of dye injected in grams
and y = diluting factor involved by the addition of anticoagulant.

$$(2)\ \text{B.V.} = \frac{\text{P.V.} \times 100}{100 - b}$$

where B.V. = blood volume
P.V. = plasma volume
and b = average haematocrit reading.

Description and comparison of methods. For the early experiments, in which congo red was used, the dye was prepared as a 1 per cent. solution made up from sterile ampoules of 0·1 g. and companion ampoules of 10 ml. of sterile doubly distilled water. The dye was injected in the following dosage:

Infants, 2 ml. of the 1 per cent. solution, i.e. 20 mg.
1- 4 yrs., 3 ml. of the 1 per cent. solution, i.e. 30 mg.
4-12 yrs., 4 ml. of the 1 per cent. solution, i.e. 40 mg.

Standards were prepared for each ampoule of the dye, 1 ml. of the 1 per cent. solution being used to prepare dilutions ranging from 1 in 30,000 to 1 in 100,000, and the photoelectric readings were graphed against these dilutions. A green filter (Ilford No. 3) was used in the absorptiometer for all congo red samples. Although it was realized that solutions of congo red in water and of congo red in plasma gave slightly different absorption curves (Heilmeyer, 1929), water was used in making up the congo red standards in all instances. In the later estimations using Evans blue, however, blood bank plasma was used for the standards.

For the Evans blue method the dye was obtained as a non-sterile powder and dissolved in distilled water to make 0·5, 0·2, and 0·1 per cent. solutions, which were thereafter sterilized by Seitz filtration. The amount injected varied between 0·5 and 0·8 mg. per kg. of body weight, as amounts within these limits were found to give suitable dilutions in

the plasma for reading on the photoelectric colorimeter. Fresh Evans blue solutions were prepared every four or five weeks, and for each batch of fresh solutions, standards were prepared in blood bank plasma and the photoelectric readings graphed. It was found that within that time interval no appreciable change in the light absorption of the solutions took place. For the preparation of these standards, the technique was the same as that followed for the dye injections; the same syringe was used, and it was always rinsed out once. Thereafter the dilutions were prepared with a standard volumetric flask and an accurate burette. Plasma was used for dilution of the standards since it had been shown that the absorption curve of Evans blue dilutions in plasma differed from that of the same dilutions in normal saline (Kennedy and Millikan, 1938; Gregersen and Gibson, 1937). This finding was confirmed by the author. The small reading due to the plasma alone was, of course, deducted from the reading obtained for each dilution before construction of the graph. Readings were taken as a routine with an orange filter (Ilford No. 5), as this filter was found to give the maximum deviation of the galvanometer with Evans blue and the minimum with haemoglobin. When haemolysis was present in the dyed specimen, which fact was obvious to the naked eye from the purplish tinge of the plasma, a reading was also taken with a blue filter (Ilford No. 1), which gave maximum light absorption with haemoglobin and minimum with Evans blue. The photoelectric reading obtained with the orange filter could then be corrected for the small reading due to the contained haemoglobin by applying a formula similar to that described by Gibson and Evelyn (1938). The need for this adjustment actually occurred very seldom.

Excretion of dye. Excretion of both congo red and Evans blue takes place via the reticulo-endothelial system and the biliary tract (Gibson and Gregersen, 1935). The disappearance rate of Evans blue from the plasma was calculated from the data obtained for the two older children, who were investigated by the multiple sampling method, and was found to be 4 and 11 per cent. respectively in the first hour following injection. In adult subjects Noble and Gregersen (1946) found the average disappearance rate to be 7·8 per cent., while in dogs Gregersen and Rawson (1943) obtained the average figure of 8·8 per cent. for the loss of Evans blue.

The practice of basing the calculation of the plasma volume on the concentration of dye found in a single specimen of plasma has been much criticized for two reasons. First, there is the difficulty of judging the time required for thorough mixing of the dye solution with the blood stream; secondly, some of the dye may be removed from the circulation during the time allowed for mixing to take place. The choice of ten minutes as the mixing time has been justified by the result of the two experiments already mentioned (fig. 1). The actual amount of dye eliminated from the circulation during this time is in fact negligible. The method of withdrawing several samples of blood at intervals following the dye injection has the advantage that in a time-concentration graph the line drawn through the values which constitute the 'disappearance slope' can be extrapolated to the ordinate in order to obtain the theoretical dilution of the dye in the plasma provided mixing could be complete at the time of injection. When this 'zero' concentration of the dye was calculated from the two multiple sampling experiments, and compared with the values observed after ten minutes, it was found that only 0·4 per cent. and 1 per cent. respectively of the dye had been excreted during the mixing time. It will thus be obvious that, by calculating the plasma volume from the single sample taken after ten minutes, the error involved will be not greater than 1 or 2 per cent. The alternative was to take from each child multiple specimens, extrapolate the 'disappearance slope,' and obtain the theoretical zero-time concentration of the dye. For technical and humane reasons this method was rejected when dealing with children.

Experimental accuracy. In order to test the reliability of the methods under similar conditions, plasma volume estimations were repeated in two children after an interval of three weeks in one and one week in the other, using congo red and Evans blue respectively. In both instances the duplicate estimations gave almost identical results, allowing for change of weight in the interval (table 1) (a).

TABLE 1
PLASMA VOLUME ESTIMATIONS

	Case No.	Date	Dye	Weight (kg.)	Plasma Volume (ml.)		Deviation (per cent.)	
					Total	per kg.	Total	per kg.
a.	66	5.10.45	C.R.	28·4	1,659	58·4		
		1.11.45	C.R.	27·68	1,618	58·4	−2·4	0
	52	31.1.47	E.B.	21·32	1,058	49·6		
		7.2.47	E.B.	21·52	1,066	49·6	+0·7	0
b.	139	8.3.46	E.B.	17·4	1,191	68·4		
		13.3.46	C.R.	17·5	1,256	71·7	+5	+4
	93	9.5.46	E.B.	23·5	1,288	54·8		
		23.5.46	C.R.	22·5	1,216	54·8	−5·5	0
	62	15.4.46	E.B.	22·4	1,149	51·3		
		23.5.46	C.R.	22·6	1,272	56·3	+10	+9

(a) = Duplicate plasma volume estimations in two children, in one case using congo red and in the other Evans blue.
(*b*) = Plasma volume estimations with congo red and with Evans blue in the same subject (three cases).

E.B. = Evans blue.
C.R. = congo red.

In spite of the advantages possessed by Evans blue, mainly because of its colour, and which have been discussed previously, it was found in practice that the results of plasma volume estimations using each dye, congo red and Evans blue, agreed within 10 per cent. (table 1) (b). When the individual results for plasma volume per kg. of the entire series were

compiled according to the dye used, no significant discrepancy was detected. Each group had a similar range of variation and the averages were very close (table 2). For these reasons the results

TABLE 2
COMPARISON OF CONGO RED RESULTS WITH EVANS BLUE RESULTS

	Congo red	Evans blue
Number of cases	23	57
Average plasma volume ml. per kg.	46·6	48·3
Range of plasma volume ml. per kg.	36·8–58·4	35·8–58
Standard deviation	6·7	5·57
Difference between averages	1·7	
Standard error of difference	1·58	

obtained by the use of congo red have been grouped together with those obtained with Evans blue, the series thereby gaining the advantage of having a greater number of estimations for consideration.

Results

The individual results are shown in detail in tables 3 to 9, but for ease of reference the average plasma and blood volumes per kg. for each age period have been collected in table 10.

TABLE 10
THE PLASMA AND BLOOD VOLUME OF HEALTHY CHILDREN
(Average values for each year of life up to 13 years)

Age	No. of Cases	Plasma volume (ml.)	Blood volume (ml.)
1 day*	1	180	418
Up to 3 mths.	1	213	359
4–6 mths.	3	273	487
7–9 ,,	3	338	574
10–12 ,,	3	379	623
1–2 yrs.	6	502	857
2–3 ,,	6	547	956
3–4 ,,	6	625	1,090
4–5 ,,	6	752	1,316
5–6 ,,	6	855	1,500
6–7 ,,	6	913	1,535
7–8 ,,	6	1,083	1,902
8–9 ,,	6	1,092	1,898
9–10 ,,	6	1,292	2,288
10–11 ,,	6	1,297	2,317
11–12 ,,	5	1,495	2,682
12–13 ,,	5	1,304	2,397

* The one-day old baby included in the table was not a healthy child, but had haemolytic disease of the newborn. The infant weighed 3·79 kg. and measured 52 cm. The blood findings were as follows: Hb. 13·6 g. per cent.; red blood cells, 4,900,000 per c.mm. of blood; and haematocrit reading 57 per cent. It was therefore concluded that the degree of haemolysis was slight, and the blood volume result has been used for the above table to complete the series of normal children.

Influence of age. On the first day of life the plasma volume was found to be 180 ml. (one case only), while at the end of the first year it had increased to approximately double this level. Thereafter the rate of increase was more gradual, a figure of about 1½ litres being attained by 13 years. The total blood volume seemed to be relatively high at birth (418 ml. in the newborn baby investigated); it fell in the following three months to about 360 ml., and by the end of the first year was approximately 150 per cent. of the birth value. In the following years it showed a steady increase with advancing age to about 2½ litres at 13 years. The difference ascertained in the behaviour of the plasma and blood volume in the first three months of life is of some interest. During this period the plasma volume increased, whereas the blood volume decreased. These facts indicate a considerable loss in the cell volume between birth and the third month, and can be correlated with the fall in haemoglobin values and red cell counts which are known to occur during the same period. The average figures quoted represent a gradual and steady increase in the plasma and blood volume from the first year onwards. The individual results, however, show that a wide variation existed between children of the same age group, due to considerable difference in body size within each group.

When expressed in relation to height and surface area (unit volume per cm. and per sq. m.), the volume of plasma and of blood increased gradually along with advancing age. (The calculation of the surface area from the weight and height of each child was based on the formula of Du Bois and Du Bois, 1916.) In contrast to these findings, unit volumes per kg. did not show any significant variation from age group to age group. Morse et al. (1947), in a comprehensive study of the blood volume in seventy-five children ranging from infancy to seventeen years, found that the values for plasma and blood volumes per kg. showed a very slight tendency to increase with growth during these years, but they regarded this increase as of questionable significance.

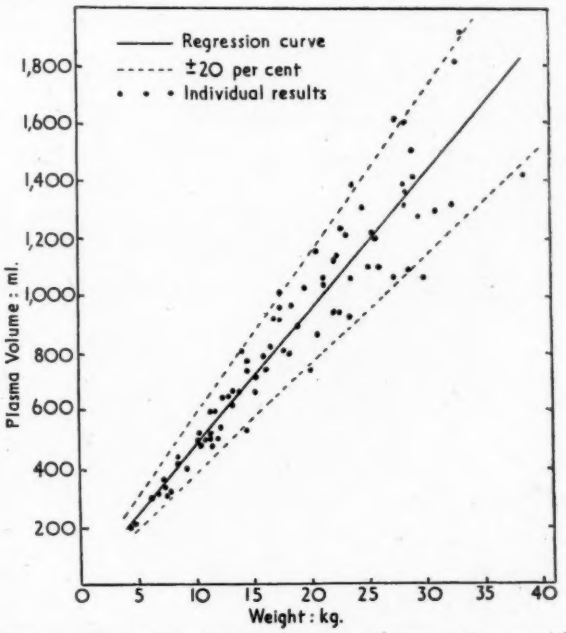

FIG. 2.—Showing the increase in plasma volume with increase in weight.

TABLE 3

HEALTHY INFANTS: 3 TO 11 MONTHS OLD

Case	Sex	Age (mths.)	Weight		Height		Hb	RBC	PCV	Plasma volume (ml.)				Blood volume (ml.)			
			kg.	% Exp. wt.	cm.	% Exp. ht.				Total	per kg.	per cm.	per sq. m.	Total	per kg.	per cm.	per sq. m.
*1	F.	3	4·305	84	57	99	9·5	4·6	41	213	49·5	3·74	850	359	83·4	6·30	1,433
*2	M.	4	4·68	84	58·5	96	10·6	4·27	45	212	45·4	3·62	805	383	81·9	6·55	1,454
*3	M.	5	6·22	100	62·5	97	10·2	4·92	47	300	48·2	4·80	954	569	91·4	9·10	1,811
4	F.	6	7·675	110	64	101	10·9	4·30	40	306	39·8	4·78	880	510	66·4	7·97	1,467
AVERAGE		4–6								273	47·8	4·30	879	487	79·9	7·87	1,577
5	M.	7	6·73	92	64	99	11·0	4·30	39	316	47·0	4·94	961	518	77·0	8·09	1,574
6	M.	7	7·16	98	66	100	10·1	4·40	41	362	50·6	5·49	1,047	614	85·7	9·30	1,776
7	M.	9	7·16	86	73	106	10·7	4·50	43	337	47·1	4·62	906	591	82·6	8·10	1,588
AVERAGE		7–9								338	48·2	5·02	971	574	81·8	8·50	1,646
8	M.	10	9·095	109	75	108	9·4	3·80	41	402	44·2	5·36	958	681	74·9	9·08	1,623
9	F.	10	8·635	103	75	108	10·4	4·20	36	419	48·6	5·59	1,021	655	75·9	8·73	1,596
10	M.	11	7·91	87	70	95	10·0	4·50	40	317	40·1	4·53	842	533	67·4	7·62	1,416
AVERAGE		10–12								379	44·3	5·16	940	623	72·7	8·47	1,545

* in tables 3-9 indicates congo red.
Hb.=haemoglobin in g. per cent. RBC=red blood count, millions per c.mm. PCV=haematocrit reading, per cent.

TABLE 4

HEALTHY INFANTS: 1 TO 3 YEARS OF AGE

Case	Sex	Age (yrs.)	Weight		Height		Hb	RBC	PCV	Plasma volume (ml.)				Blood volume (ml.)			
			kg.	% Exp. wt.	cm.	% Exp. ht.				Total	per kg.	per cm.	per sq. m.	Total	per kg.	per cm.	per sq. m.
*11	F.	1	11·49	102	87	107	12·8	4·06	46	479	41·7	5·51	970	880	76·6	10·11	1,775
12	F.	1	8·61	93	76	103	11·0	4·2	38	435	50·5	5·72	1,051	701	81·4	9·23	1,694
13	F.	1	10·26	102	79	103	10·9	4·2	39	483	47·1	6·12	1,052	793	77·3	10·03	1,728
14	F.	1	11·08	110	82	105	10·0	4·2	39	516	46·6	6·29	1,058	846	76·4	10·31	1,735
15	F.	1	10·75	95	86	105	12·5	4·6	39	499	46·4	5·80	1,001	817	76·0	9·50	1,639
16	M.	1	11·31	100	87·5	110	12·2	4·65	46	598	52·9	6·84	1,161	1,108	98·0	12·66	2,150
AVERAGE		1–2					11·9	4·32	41	502	47·5	6·05	1,049	857	80·9	10·31	1,787
17	F.	2	11·92	94	89	103	11·2	4·54	43	599	50·3	6·73	1,124	1,052	88·2	11·81	1,969
18	F.	2	10·24	84	87	103	11·8	4·40	41	520	50·7	5·97	1,057	880	86·0	10·12	1,791
19	F.	2	10·12	87	88	105	13·4	4·95	44	500	49·4	5·68	1,015	892	88·1	10·14	1,811
20	M.	2	11·2	86	87	100	13·3	4·85	47	506	45·2	5·82	991	954	85·2	10·97	1,868
21	M.	2	12·52	95	95	105	12·1	4·60	41	653	52·2	5·88	1,143	1,108	88·4	11·65	1,937
22	M.	2	11·8	95	90·5	107	12·9	4·70	41	503	42·6	5·56	935	852	72·2	9·42	1,584
AVERAGE		2–3					12·4	4·67	43	547	48·4	6·17	1,044	956	84·7	10·68	1,827

TABLE 5

HEALTHY CHILDREN: 3 TO 5 YEARS OF AGE

Case	Sex	Age (yrs.)	Weight		Height		Hb	RBC	PCV	Plasma volume (ml.)				Blood volume (ml.)			
			kg.	% Exp. wt.	cm.	% Exp. ht.				Total	per kg.	per cm.	per sq. m.	Total	per kg.	per cm.	per sq. m.
*23	M.	3	15·24	102	100	108	10·3	4·2	44	723	47·4	7·20	1,120	1,289	84·6	12·90	2,001
*24	F.	3	13·08	96	94	106	12·1	4·6	45	623	47·7	6·63	1,079	1,141	87·3	12·14	1,976
*25	M.	3	13·9	98	93	105	10·4	4·14	40	673	48·4	7·20	1,140	1,127	81·1	12·06	1,909
26	M.	3	13·06	85	100	107	12·5	4·88	42	671	51·4	6·71	1,113	1,156	88·6	11·56	1,916
27	M.	3	12·32	84	99	108	10·1	4·2	42·5	535	43·4	5·41	918	931	75·5	9·40	1,596
28	F.	3	14·42	96	97	102	10·2	4·5	41	527	36·6	5·44	855	894	62·0	9·21	1,450
AVERAGE		3–4					10·9	4·42	42·4	625	45·8	6·43	1,037	1,090	79·8	11·21	1,808
29	F.	4	12·98	80	93	92	12·1	4·7	39	662	51·0	7·12	1,157	1,085	83·6	11·67	1,897
30	M.	4	14·64	84	100	99	12·8	4·9	44	777	53·0	7·77	1,226	1,388	94·7	13·88	2,191
31	F.	4	14·24	85	101	100	13·4	4·3	41	806	56·6	7·95	1,277	1,367	96·0	13·47	2,163
32	F.	4	16·24	104	105	107	13·1	4·8	44	735	45·3	6·97	1,068	1,312	80·8	12·44	1,905
33	F.	4	14·62	95	96	97	13·0	4·7	45	737	50·4	7·68	1,202	1,341	91·7	13·96	2,187
34	M.	4	15·96	100	103	103	13·0	4·98	44	793	49·7	7·69	1,182	1,403	87·9	13·62	2,091
AVERAGE		4–5					12·9	4·73	43	752	51·0	7·53	1,185	1,316	89·1	13·17	2,072

TABLE 6—HEALTHY CHILDREN, 5 TO 7 YEARS OF AGE

Case	Sex	Age (yrs.)	Weight kg.	Weight % Exp. wt.	Height cm.	Height % Exp. ht.	Hb.	RBC	PCV	Plasma volume (ml.) Total	per kg.	per cm.	per sq. m.	Blood volume (ml.) Total	per kg.	per cm.	per sq. m.
*35	M.	5	18·4	90	111·5	100	10·1	3·9	38	797	43·3	7·15	1,055	1,288	70·0	11·55	1,706
*36	M.	5	16·74	90	108	102	13·0	4·96	44	818	48·9	7·57	1,153	1,466	87·6	13·57	2,068
37	M.	5	16·98	84	107	99	11·6	4·75	42	920	54·2	8·64	1,299	1,587	93·4	14·83	2,242
38	F.	5	15·17	85	108	103	13·0	4·6	42	672	44·3	6·22	989	1,158	76·4	10·73	1,704
39	F.	5	18·54	100	120	110	12·6	4·85	43	971	52·4	8·09	1,213	1,703	91·9	14·19	2,127
40	F.	5	22·12	110	116	105	14·9	4·98	47	954	43·1	8·22	1,133	1,799	81·3	15·51	2,139
AVERAGE		5–6					12·5	4·67	42·7	855	47·7	7·65	1,140	1,500	83·4	13·40	1,998
*41	M.	6	17·54	82	140	122	10·0	4·54	43	960	54·7	6·86	1,100	1,678	95·7	11·99	1,923
*42	F.	6	19·96	92	114·5	98	11·4	4·23	44	739	37·0	6·45	926	1,316	66·0	11·50	1,650
*43	F.	6	17·2	83	109·5	96	11·9	4·4	45	921	53·6	8·41	1,271	1,406	81·8	12·84	1,939
44	F.	6	17·52	88	117	105	10·5	4·1	39	1,016	58·0	8·69	1,328	1,666	95·1	14·24	2,178
45	M.	6	19·74	93	114·5	100	11·1	4·45	42	1,027	52·0	8·97	1,293	1,770	89·7	15·46	2,230
46	F.	6	17·88	89	113	101	10·3	4·1	41	812	45·4	7·18	1,079	1,376	76·9	12·17	1,828
AVERAGE		6–7					10·9	4·3	42·3	913	50·1	7·76	1,166	1,535	84·2	13·03	1,958

TABLE 7—HEALTHY CHILDREN, 7 TO 9 YEARS OF AGE

Case	Sex	Age (yrs.)	Weight kg.	Weight % Exp. wt.	Height cm.	Height % Exp. ht.	Hb	RBC	PCV	Plasma volume (ml.) Total	per kg.	per cm.	per sq. m.	Blood volume (ml.) Total	per kg.	per cm.	per sq. m.
*47	M.	7	20·68	90	118·5	100	11·2	4·0	40	1,161	56·1	9·80	1,315	1,935	93·5	16·32	2,192
48	F.	7	25·06	108	125	104	12·7	4·7	46	1,105	44·0	8·84	1,181	2,046	82·0	16·37	2,189
49	F.	7	18·96	85	112	95	11·9	4·6	41	904	47·7	8·07	1,177	1,532	80·8	13·68	1,994
50	F.	7	21·4	95	125	105	13·6	4·9	46	1,050	49·1	8·40	1,201	1,945	90·9	15·55	2,225
51	M.	7	23·32	102	124	103	13·6	4·75	41	1,222	52·4	9·86	1,357	2,071	88·8	16·70	2,299
52	M.	7	21·32	91	118	99	13·6	4·85	45	1,058	49·6	8·97	1,263	1,923	90·2	16·30	2,296
AVERAGE		7–8					13·3	4·63	43	1,083	49·8	8·99	1,249	1,902	87·7	15·82	2,365
*53	F.	8	20·8	81	124·5	99	10·7	4·43	45	869	41·8	6·98	1,008	1,576	75·8	12·66	1,828
54	M.	8	26·0	105	127	104	12·5	4·85	43	1,101	42·4	8·67	1,147	1,932	74·3	15·21	2,010
55	F.	8	23·64	98	126·5	103	11·6	4·8	42	933	39·5	7·38	1,014	1,609	68·1	12·72	1,747
56	F.	8	25·36	100	131	105	13·6	4·94	42·5	1,211	47·7	9·24	1,245	2,105	83·0	16·07	2,164
57	F.	8	22·28	87	123	98	12·6	4·61	42	1,132	50·8	9·20	1,287	1,952	87·6	15·87	2,219
58	M.	8	24·56	99	129	102	14·2	4·8	41	1,307	53·2	10·14	1,378	2,216	90·2	17·18	2,336
AVERAGE		8–9					12·5	4·74	42·6	1,092	45·9	8·60	1,180	1,898	79·8	14·95	2,051

TABLE 8—HEALTHY CHILDREN, 9 TO 11 YEARS OF AGE

Case	Sex	Age (yrs.)	Weight kg.	Weight % Exp. wt.	Height cm.	Height % Exp. ht.	Hb	RBC	PCV	Plasma volume (ml.) Total	per kg.	per cm.	per sq. m.	Blood volume (ml.) Total	per kg.	per cm.	per sq. m.
*59	M.	9	25·8	88	133·5	102	10·2	4·24	44	1,204	46·6	9·02	1,210	2,156	83·6	16·14	2,158
*60	M.	9	23·76	89	126	99	12·3	4·27	48	1,388	58·4	11·02	1,509	2,695	113·0	21·39	2,930
*61	F.	9	22·56	82	132	103	10·6	4·62	44	940	41·7	7·12	1,009	1,681	74·5	12·74	1,804
62	F.	9	22·4	81	124·5	96	10·0	4·1	40	1,149	51·3	9·23	1,293	1,900	84·8	15·26	2,136
63	M.	9	32·84	110	142·5	110	10·8	4·7	43	1,822	55·5	12·78	1,577	3,196	97·3	22·43	2,766
64	M.	9	22·92	82	128	100	13·4	4·8	41	1,239	54·0	9·68	1,354	2,099	91·6	16·40	2,295
AVERAGE		9–10					11·2	4·45	43	1,290	51·2	9·81	1,325	2,288	90·8	17·39	2,348
*65	F.	10	28·6	92	135	100	12·0	4·75	42	1,088	38·1	8·06	1,040	1,890	66·1	14·01	1,804
*66	F.	10	27·68	87	144	106	11·6	4·68	41	1,618	58·4	11·24	1,520	2,737	99·0	19·01	2,570
*67	F.	10	30·96	106	138	104	10·2	4·62	43	1,304	42·1	9·45	1,242	2,296	74·1	16·64	2,184
68	M.	10	29·1	96	127	96	12·7	4·63	45	1,416	48·6	11·15	1,404	2,575	88·5	20·28	2,554
69	M.	10	23·68	80	130	98	12·5	4·7	47	1,074	45·4	8·27	1,145	2,027	85·6	15·60	2,160
70	F.	10	29·64	94	140	100	13·8	4·8	46	1,283	43·3	9·17	1,180	2,378	80·2	16·98	2,184
AVERAGE		10–11					12·1	4·69	44	1,297	45·9	9·55	1,255	2,317	82·2	17·09	2,243

TABLE 9—HEALTHY CHILDREN, 11 TO 13 YEARS OF AGE

Case	Sex	Age (yrs.)	Weight kg.	Weight % Exp. wt.	Height cm.	Height % Exp. ht.	Hb,	RBC	PCV	Plasma volume (ml.) Total Total	per kg.	per cm.	per sq. m	Blood volume (ml.) Total	per kg.	per cm.	per sq. m.
*71	F.	11	27·32	83	137	99	11·8	4·2	45	1,068	39·1	7·81	1,032	1,945	71·2	14·23	1,879
72	M.	11	33·08	98	146	105	11·7	4·6	42	1,918	57·9	13·15	1,629	3,296	99·6	22·57	2,800
73	F.	11	28·28	83	138	98	13·8	4·8	46	1,606	56·8	11·63	1,516	2,974	105·2	21·55	2,806
74	F.	11	29·0	87	135	97	14·6	4·9	45	1,514	52·2	11·21	1,460	2,752	94·9	20·39	2,641
75	M.	11	28·46	84	133	97	13·1	4·85	44	1,367	48·0	10·28	1,325	2,441	85·8	18·35	2,367
AVERAGE		11–12					13·0	4·67	44	1,495	50·8	10·82	1,392	2,682	91·3	19·42	2,499
*76	M.	12	28·4	80	139	98	12·0	4·70	46	1,322	47·5	9·51	1,250	2,441	87·7	17·56	2,308
*77	M.	13	38·75	102	151	104	12·2	4·2	47	1,424	36·8	9·43	1,103	2,683	69·2	17·77	2,076
78	M.	12	32·46	90	147	100	13·5	4·86	46	1,320	40·7	8·98	1,125	2,445	75·3	16·63	2,083
79	F.	12	29·8	80	145	100	14·0	4·9	48	1,066	35·8	7·35	950	2,049	68·8	14·14	1,828
80	F.	12	28·28	80	141	98	12·9	4·6	39	1,390	49·2	9·86	1,293	2,278	80·6	16·15	2,120
AVERAGE		12–13					12·9	4·65	45	1,304	42·0	9·05	1,210	2,379	76·3	16·45	2,207

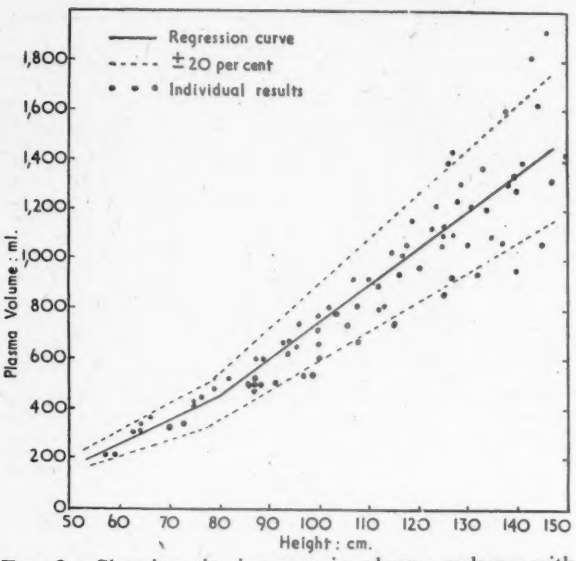

FIG. 3.—Showing the increase in plasma volume with increase in height.

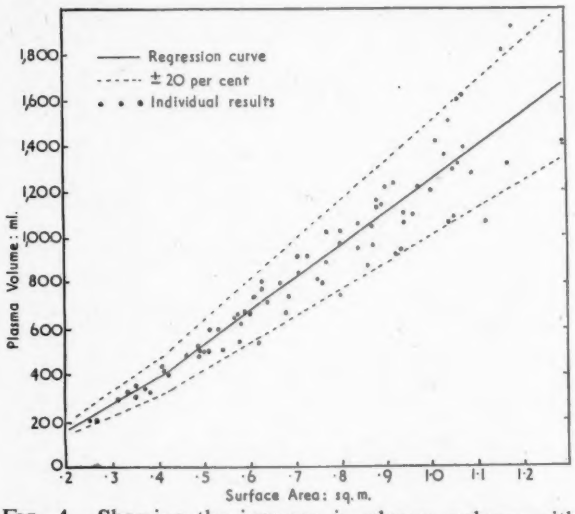

FIG. 4.—Showing the increase in plasma volume with increase in body surface.

Influence of body size. Weight, height, and surface area bear a closer relationship to plasma and blood volume than does age. It was noted in the scatter diagrams (figs. 2 to 7) that, while the plasma and blood volumes in general showed an increase with growth in these measurements, the individual results occupied a fairly wide range round the average. During analysis of the eighty cases, calculation of the coefficient of correlation gave the results in table 11.

TABLE 11
COEFFICIENT OF CORRELATION

	Plasma		Blood	
	Correlation coefficient	Standard error	Correlation coefficient	Standard error
Weight ..	+0·9513	0·1125	+0·9563	0·1125
Surface area ..	+0·9344	,,	+0·9506	,,
Height ..	+0·9266	,,	+0·9305	,,

Weight gave the highest degree of correlation for both plasma and blood volumes but was followed closely by surface area and height in that order. The regression equations based on these results were used to form the average lines in figs. 2 to 7 (table 12).

TABLE 12
REGRESSION EQUATIONS

	Plasma volume	Blood volume
Weight	P.V. = 46·87 Wt. + 15·5	B.V. = 85·27 Wt. − 25
Surface area	P.V. = 1,433 S.A. − 186·5	B.V. = 2,638 S.A. − 415
Height	P.V. = 14·71 Ht. − 725·5	B.V. = 26·74 Ht. − 1,369

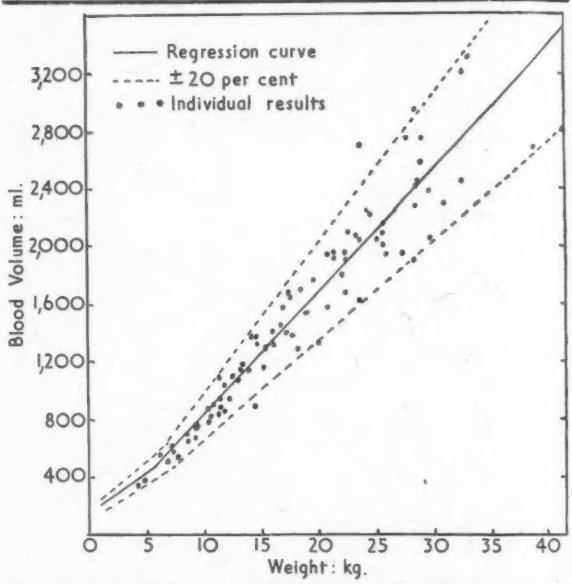

FIG. 5.—Showing the increase in blood volume with increase in weight.

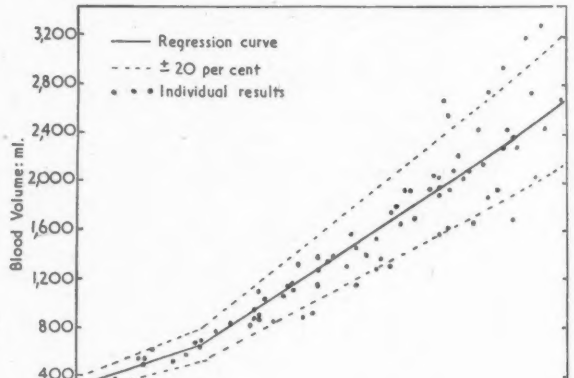

FIG. 6.—Showing the increase in blood volume with increase in height.

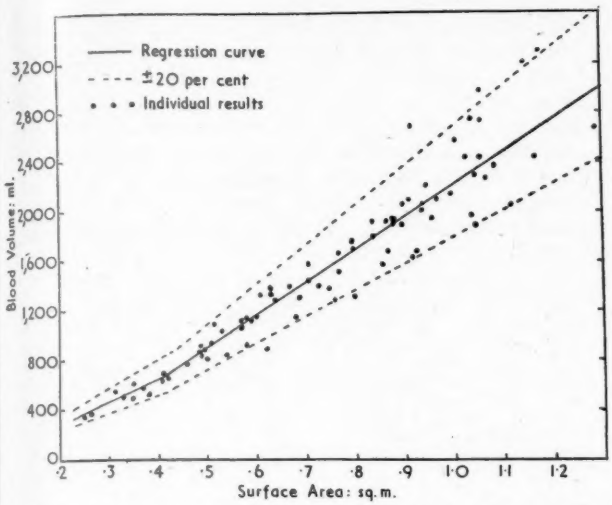

FIG. 7.—Showing the increase in blood volume with increase in surface area.

It was discovered, in comparing the plasma volume figures obtained by using the three regression graphs with the values found by actual experiment, that those obtained from the weight graph gave a better or as good an approximation as the other two in thirty-eight of the eighty cases. Similarly, using the height graph this figure was twenty-eight, while for the surface area graph it was twenty-two. From the above data it was concluded that within the scope of the present series, that is, in children up to 13 years of age, weight formed the most reliable basis on which to calculate the blood volume.

Discussion

In the analysis of these results, certain important findings emerged and it will be helpful to discuss these in greater detail. Certain differences were also evident when comparing the studies with those of other workers.

Infants. Earlier reports on the blood volume in children under one year have recorded the use of the dye brilliant vital red with the following results. Lucas and Dearing (1921) found the average figure for blood volume per kg. to be 109 ml., Bakwin and Rivkin (1924) found it to be 101 ml., and Seckel (1936) 83 ml. McIntosh (1929), using the carbon monoxide method, found the blood volume in children up to two years to be on the average, 77 ml. per kg., a result which agrees closely with the mean of the present series for the group of ten infants, namely 78·7 ml. per kg. The only other publication found, which included infants under one year, investigated by the Evans blue method, gave the figure of 73·6 ml. per kg. (Brines et al. 1941).

The average figure of the author's studies for plasma volume in infants was shown to be 46·1 ml. per kg. Darrow et al. (1928) found that during the first year the figures for plasma volume per kg. rose from 50 to 62 ml. and slowly returned to 50 by the fourth year, after which the level remained constant. The results for the infants studied in the present series, however, did not conform to this trend, the values for plasma volume when related to weight

TABLE 13
GROUP REGRESSION EQUATIONS

	Plasma		Blood	
	Volume	Coefficient of correlation	Volume	Coefficient of correlation
WEIGHT (kg.)				
3–10	P.V. = 40·22 Wt. + 43	+0·8424	B.V. = 58·2 Wt. + 142	+0·8037
10–20	P.V. = 49·62 Wt. − 14	+0·881	B.V. = 82·7 Wt. + 17	+0·8732
20–30	P.V. = 54·25 Wt. − 167	+0·7698	B.V. = 95·7 Wt. − 274	+0·861
SURFACE AREA (sq.m.):				
0·2–0·5	P.V. = 1,147 S.A. − 67	+0·913	B.V. = 1,907 S.A. − 99	+0·9101
0·5–0·9	P.V. = 1,362 S.A. − 150	+0·870	B.V. = 2,489 S.A. − 346	+0·9189
0·9–1·3	P.V. = 1,157 S.A. + 114	+0·464	B.V. = 2,605 S.A. − 350	+0·665
HEIGHT (cm.):				
50–75	P.V. = 8·44 Ht. − 243	+0·8115	B.V. = 13·33 Ht. − 345	+0·8
75–100	P.V. = 10·77 Ht. − 398	+0·730	B.V. = 21·81 Ht. − 969	+0·7661
100–125 .. .	P.V. = 16·58 Ht. − 965	+0·704	B.V. = 33·13 Ht. − 2,182	+0·7691

In order to ascertain if these equations calculated from the series as a whole could be relied upon to give a reasonable estimate of the plasma or blood volume for the individual age groups of children studied, the regression equations were formed for small groups of the results (table 13).

As the correlation coefficients for the group 125-150 cm. were not significant, regression equations were not calculated.

When plotted on the same graphs as the general equations, it was found that these sectional regression equations corresponded very well with the average trends, except in the case of the youngest children, for whom plasma and blood volumes calculated from the general equations were considerably lower than those found by experiment. To rectify this error, the regression lines for the groups up to 10 kg., 75 cm., and 0·5 sq. m., have been substituted for the lowest parts of the general regression graphs drawn for weight, height, and surface area respectively (except in the graph for plasma volume and weight, where correction of the general equation was not required).

occupying the same range of variation as was found throughout the entire series. The idea that fluctuations in body weight in infants were often due to changes in the water content of the tissues and not to real tissue growth or loss was adduced by Bakwin and Rivkin (1924) to explain their finding that wide variations existed in the plasma volume in normal infants (range 38 to 72 ml. per kg., average 60·5 ml. per kg.). For the infants of the present investigation the average plasma volume calculated was 46·1 ml. per kg. with a range of 39·8 to 50·6 ml., results which are similar to those for this series as a whole. In a healthy infant on an adequate caloric and fluid intake and in the absence of diarrhoea, vomiting, and fever, there is no justification, in the present results at least, for postulating an unstable system of fluid exchange between tissues and plasma.

Older children. To facilitate comparison with the present studies the results published by other authors of blood volume investigations in older children have been collected and tabulated (table 14). No

TABLE 14
PUBLISHED RESULTS FOR PLASMA AND BLOOD VOLUME

Plasma volume	Age in Years	No. of Cases	Range	Plasma volume (ml. per kg.) Mean	Standard Deviation
Brines et al., 1941†	0–17	50	32–55·4	41·8	5
Schlutz et al., 1940					
(1)	12–15	7	39·5–56·8	45	6·2
(2)	16–17	9	40·1–60·2	47·2	6·7
Morse et al., 1947*†	1–13	40	42–66·8	50·1	5·74
Author's series ..	0–13	80	35–58·4	47·8	5·83
BLOOD VOLUME					
Brines et al., 1941†	0–17	50	46·5–95·9	69·8	9·64
Schlutz et al., 1940					
(1)	12–15	7	64·9–103·1	78·8	12·0
(2)	16–17	9	72·4–104·5	85·3	11·7
Morse et al., 1947*†	1–13	40	68·7–111·5	84·1	9·16
Author's series ..	0–13	80	62–113	83·5	10·39

* Only the first forty children of this series of seventy-five have been quoted as they corresponded in age to the present series.
† The spontaneous deviations supplied for the series of Brines et al. and Morse et al. have been calculated from the authors' figures.

significant differences were found, with the exception that those of Brines et al. (1941) were lower than all the others.

The steady increase of plasma and blood volume with advancing age in childhood has already been discussed. Periods of excessive rise in blood volume have been described by Seckel (1936), who thought that relatively high values were obtained at two periods during childhood, namely between 3 and 6 years, and between 11 and 13. There was no indication of this phenomenon in the present studies.

Sex differences. It has been shown that adult women tend to have both a lower absolute plasma and unit plasma volume than adult men of the same weight due to their greater proportion of fat over tissues rich in blood (Gibson and Evans, 1937b). A greater difference was observed between the sexes as regards absolute blood volume, due in part to the discrepancy in plasma volume, but mainly to the greater values found in men for the red cell volume. The present series was therefore divided into its component groups of thirty-eight boys and forty-two girls, and analysed in search of any differences attributable to sex (table 15).

TABLE 15
THE PLASMA AND BLOOD VOLUME ACCORDING TO SEX

	Plasma volume (ml. per kg.)			Blood volume (ml. per kg.)		
	Mean	Range	S.D.	Mean	Range	S.D.
38 boys ..	48·8	36·8 to 58·4	5·9	86·0	67·4 to 113·0	9·95
42 girls ..	46·9	35·8 to 58·4	5·9	81·3	62·0 to 105·2	9·38
Difference	1·9			4·7		
S.E. of difference	1·32			2·17		

S.D. = standard deviation.
S.E. = standard error.

The girls had lower average plasma and blood volumes per kg. than the boys, the difference being greater for blood volume. Although the difference was just more than twice the standard error of the difference, it was considered that it was not sufficiently great to be judged significant. The unit volumes related to height, however, also showed a tendency to run at lower levels in the group of girls than in the group of boys (fig. 8). It is therefore tentatively suggested that a sex difference in blood volume may exist in children as well as in adults,

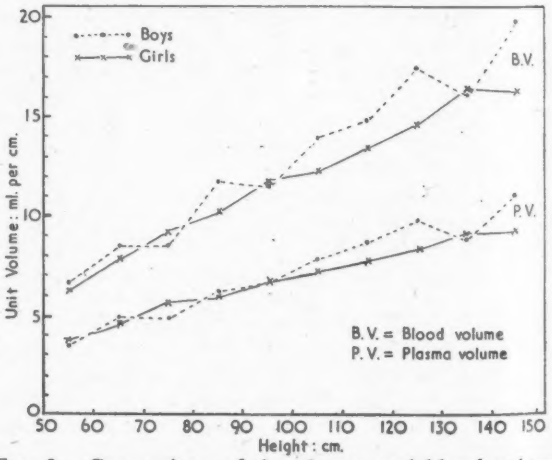

FIG. 8.—Comparison of the plasma and blood volume in boys and girls of the same height. (Each plotted figure represents the average for each group of 10 cm.)

but a much larger number of estimations would be necessary before any definite conclusion could be drawn. Brines et al. (1941), on the other hand, held the opposite opinion, namely, that there was no difference between the sexes until puberty, when boys began to have larger blood volumes than girls of the same measurements. No significant difference was found in this series, in haematocrit and haemoglobin readings, nor in red cell counts, during comparison of the two sexes.

General considerations. When the results were examined, a striking feature was noticeable, namely, the wide range within which the blood volumes of individuals of the same body size could be distributed. A reference to the diagrams (figs. 2 to 7) will show that all have several values lying outwith 20 per cent. of average. The height basis yielded the greatest number of aberrant results, as twelve of the eighty, or 15 per cent., lay outwith the 20 per cent. variation. All except one, however, were included within ± 30 per cent. This wide range of normality is in accord with the findings of other investigators (Gibson and Evans, 1937b; Morse et al., 1947).

No definite conclusions could be drawn from the present results regarding the influence of muscularity and obesity on the blood volume in individuals of comparable size. Gibson and Evans, however, concluded that in adults the absolute total blood volume was high in muscular and obese persons, and low in thin subjects. Morse and his colleagues considered that thin children tended to have a large blood volume and that both obese and undernourished children tended to have a low blood volume.

The Correlative Factor of Choice

Previous workers have held diverse opinions regarding the most suitable basis for the prediction of the blood volume of a given individual. McIntosh (1929) and Darrow et al. (1928), advocated weight as a basis of correlation, while recent investigations by Morse et al. (1947) would seem to establish surface area as giving the closest approximations to the values found by experiment. As stated previously, analysis of the present studies showed that weight provided the best correlation for both plasma and blood volume in healthy children. The soft tissues of the body, however, can undergo considerable changes in weight in such conditions as dehydration, marasmus, and oedema. As a consequence any concurrent change in plasma volume may be masked, or at least minimized, if plasma volume is expressed in relation to kg. of weight, and also to sq. m. of surface area, since any change in weight is reflected in the surface area measurement. For example, a child weighing 25 kg. and having a plasma volume of 1,250 ml. begins to show signs of congestive cardiac failure. His plasma volume may then increase by 20 per cent., or 250 ml. to become 1,500 ml. Meanwhile, his weight may increase to 26 kg. Before cardiac failure, therefore, his plasma volume was 50 ml. per kg., and after failure, 57 ml. per kg. Thus he has apparently gained 7 ml. of plasma per kg. or a total of either 175 or 182 ml. depending on whether the first or the second weight is used for the calculation. Neither of these figures approaches the extent of the true plasma increase. This type of error could, of course, be avoided by keeping the results in terms of absolute plasma or blood volume, but it is more convenient for purposes of comparison to reduce the figures to some sort of unit. It is, therefore, suggested that height should be adopted as the basis for prediction of the normal blood volume when investigating conditions of disease. For this opinion, some support has been found in the publications of other workers (Gibson and Evans, 1937b; Brines et al., 1941; Perera, 1946).

Summary

1. Plasma and blood volume investigations have been carried out in eighty healthy children. Although congo red was used in the early investigations and Evans blue in the later ones, evidence is produced to show that the results are comparable.

2. Increase in age was accompanied by increase in absolute plasma and blood volumes. Unit volumes related to height and surface area showed a rise with increasing age, while unit volumes related to weight remained unchanged.

3. Of the three measurements, weight, height, and surface area, weight bore the closest relationship to both plasma and blood volumes, judged by the correlation coefficients and the scatter of the results round the regression equations.

4. Because of the tendency of body weight to undergo rapid change, especially in children, height has been suggested as the most suitable correlation factor when comparing the plasma and blood volumes in disease with those found in health.

5. In boys, both plasma and blood volumes showed a tendency to be higher than in girls of the same size.

I wish to express my gratitude to Prof. Stanley Graham for permission to study the children in his wards, and for his advice and encouragement in preparing this paper.

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SOME ETIOLOGICAL FACTORS IN THE COELIAC SYNDROME*

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Introduction

To speak to an audience at the University of Birmingham about the coeliac syndrome, a disease which has been encountered, studied, and treated more often here than probably anywhere else in the world, and where much fundamental research into the etiology, diagnosis, treatment, and understanding of this disease has been carried on, is ' like carrying coals to Newcastle '. I refer to the many papers produced by Sir Leonard Parsons, Doctors Neale, Hickmans, and Ross, and to Professor Frazer's recent work on fat metabolism.

As pointed out by Sir Leonard Parsons in his Rachford Memorial Lectures in 1931, there is little of importance known today that would alter Gee's original description of coeliac disease. It is interesting to note that most of the present-day researches are concerned with possible abnormalities or causative factors which were mentioned by the original writers on this subject. The absence of pathological findings was noted by Gee. A possible deficiency of bile salts was considered by Cheadle in 1903, but has since been disproven. Herter in 1908 felt that coeliac disease was caused by some infection. He also drew attention to the stunted growth, and the condition is sometimes known as 'Herter's infantilism'. Schütz in 1905 thought that abnormality of the secretory and absorptive functions of the intestine was a factor. A theory suggested by Moncrieff and Payne was that the disease was due to a metabolic error similar to that occurring in diabetes. The presence of excess fat in the stools was noted by Cheadle in 1903 and has been the subject of much investigation since.

It will be noted in the observations that I am about to make that many of these possible causes are discussed again in more recent studies of the disease.

We have confined the term coeliac disease to the condition of infancy and early childhood in which there is persistent diarrhoea with foul, undigested stools which cannot be accounted for by a bacteriological or other cause. The subjects have poor appetite, fail to gain weight properly, have a protuberant abdomen, and respond to high-protein feeding. The other signs and symptoms are too well known to be dwelt upon further. Cystic fibrosis of the pancreas has not been included.

The following case record will serve to illustrate some of the usual findings in the histories of patients with coeliac disease.

Case Record

V.D. This patient, a two year old girl, was first brought to the hospital with a history of an enlarged abdomen for several months. Three months before admission she became listless and irritable with loss of appetite. Two months before admission she had five or six watery, pale, yellow stools daily; these contained many large curds. At this time the patient had lost weight, and there was considerable gas in the bowel. There were no other known cases in the family, but a grandmother and an uncle had diabetes.

The child showed marked loss of weight and the abdomen was distended and tympanitic. An oral glucose tolerance test showed a flat curve, as did the vitamin A absorption test.

Treatment consisted of a high protein diet and intramuscular injections of crude liver extract and vitamin B complex daily for three weeks. As the stools improved and the child gained weight, vitamins D and C, as well as the ferrous sulphate were added, and the child was able to go home.

One year later the child was re-admitted to the hospital following a recurrence of the condition, which had been treated in another city for three months. She was now three years old, and was found to be in an emaciated condition, weighing only fifteen pounds (fig. 1).

The condition improved after treatment with high protein diet, and in three months the picture had changed (fig. 2).

Bouts of indigestion returned with infections of the upper respiratory tract in the following two years, but she continued to grow and the digestive upsets became less severe.

* Being an Ingelby Lecture delivered before the University of Birmingham on May 20, 1948.

The Present Investigation

From 1932 to 1945 we had 150 children admitted to our institution with the diagnosis of coeliac disease. Ninety of these have been used for analysis in this report.

Fifty children suffering from so-called coeliac disease had a history of infection at the onset of their symptoms. The infection was either acute or chronic, and the following varieties were listed:

Tonsillitis	30
Otitis media	9
Nasopharyngitis	5
Acute bronchitis	4
Cystitis	1
' Intestinal influenza '	1

Many cases with an onset following tonsillitis relapsed during a recurrence of the tonsillar infection, and it is interesting to note that of twenty children who were re-admitted with a recurrence of the coeliac syndrome, eighteen showed a recurrence of the primary infection. Even after removal of tonsils and adenoids, the coeliac condition is apt to recur, but less frequently. Whether these relapses are due to the infection itself or to a generally weakened resistance, resulting from the infection, or to impaired absorption of vitamins, is still an open question. The incidence of cases with an onset associated with infection is higher, as one would expect, during the season when respiratory diseases are most common. The onset of signs and symptoms of coeliac disease occurred immediately after the infection in thirty-five of the fifty cases. Two of the children with recurrent infections had diarrhoea and vomiting from birth, until a more severe infection caused the fully developed disease. Eight cases developed gradually.

In another group, which may be called ' idiopathic coeliac disease ', are the remaining cases, in which there is no proof of any underlying infection. Many of these cases had their onset in the summer months. Of the thirty-four children in this group, eighteen showed a gradual onset of the coeliac syndrome; three cases developed gradually after birth, two developed diarrhoea when the diet was changed, while in the remainder the exact time of onset could not be determined. It is thus evident that an infection is followed usually by a rapid onset of diarrhoea, vomiting, foul, bulky stools, and general irritability. In the idiopathic cases a tendency to a gradual appearance of signs and symptoms prevails, the most common complaint being stationary or decreasing weight, soon followed by laxity of the bowels and abdominal pain due to an accumulation of gas, probably a manifestation of lowered carbohydrate tolerance which in turn follows the initial steatorrhoea.

Approximately two-thirds of the children with coeliac disease were never breast-fed. It should be noted that in infants who had been breast-fed the disease appeared on the average at sixteen months of age, while in bottle-fed infants it appeared on the average at ten months. This suggests that breast-feeding has a preventive effect or is responsible for delaying the onset of the condition. Eighty-five per cent. of the cases so tested showed a low or flat curve in one or both of the glucose tolerance and vitamin A absorption tests.

It was noted that about 50 per cent. of the children had not received vitamin C or D in the first six months of life. One must, however, view this fact with caution because we do not suppose that the absence of these vitamins is entirely the cause of coeliac disease.

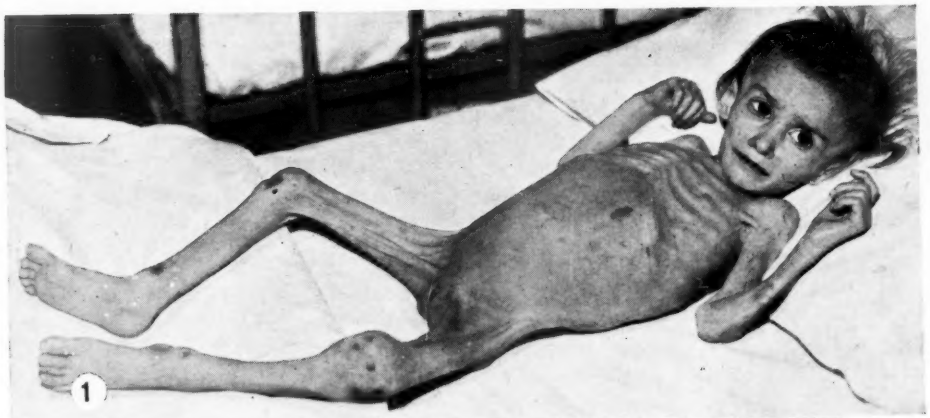
The patients were brought back to the hospital for a follow-up examination in which a careful medical, dental, and genetic study was carried out. The results of this follow-up study have revealed some interesting findings.

Dr. Milner, working under Dr. Fisk, who is in charge of orthodontics in the hospital, has made the following preliminary report of the results of the dental examination of formal coeliac patients: generally speaking these children are ' caries immune ', and their saliva tests show ' caries immunity '; they have a neutero-occlusion molar relationship, a wide dental arch, more than usual spacing when the anterior deciduous teeth are shed, and a deep overbite.

Dr. Margaret Thompson, working under Dr. Norma Ford Walker and in co-operation with Dr. Ebbs, has conducted a careful genetical investigation of ninety former coeliac patients and their families, in order to determine if coeliac disease depends in any way for its expression upon hereditary factors. She has found that these children tend to appear late in the birth rate of the family, that the average age of their mother is older than normal, and that their dermal patterns suggest possible disturbance of growth in prenatal life. In this series there were more brothers, sisters, and relatives affected than would be expected, and diabetes was a hundred times more common amongst them, fifty times more common amongst their siblings, seven times more common in their parents, and twice as common in their grandparents than in the normal population.

It seems reasonable, from the above facts, to suggest that all coeliacs are potential diabetics. ' Congenital familial steatorrhoea ' was the term given to cases described by Garrod and Hurtley in 1913 that had symptoms not unlike coeliac disease. The possible similarity to diabetes was suggested by Moncrieff and Payne (1928), who concluded that coeliac disease is a fault of malutilization of fat and not of malabsorption. McRae and Morris (1931), however, showed that there was faulty absorption of fat in patients suffering from coeliac disease, and Poynton and Cole have described a case of coeliac disease which developed diabetes mellitus.

The high incidence of digestive difficulties in the families of coeliacs led Hablutzel Weber (1923) to suggest a constitutional factor in the etiology. The



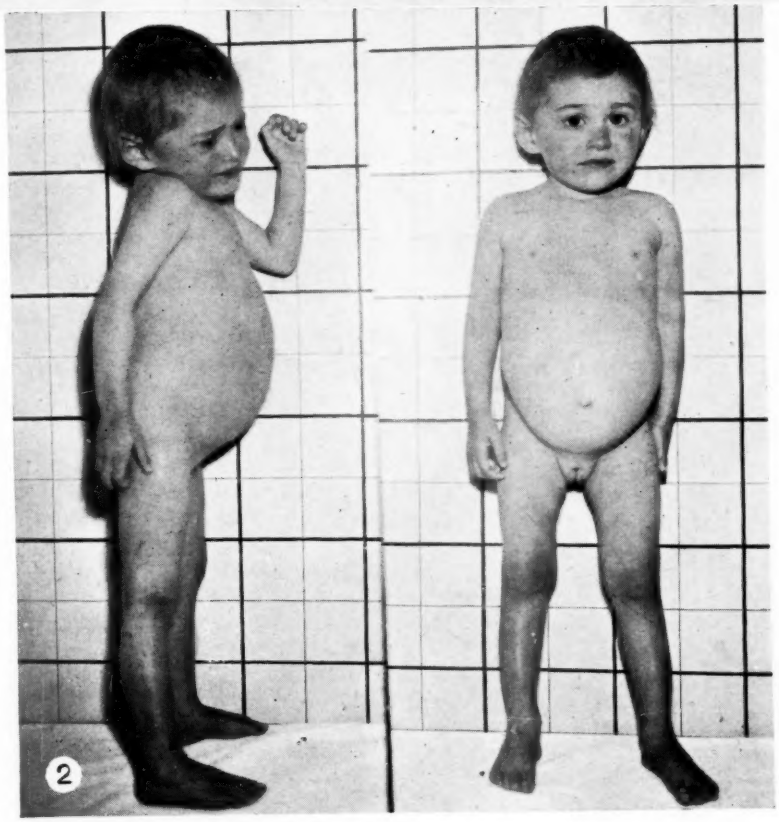


FIG. 1—Emaciated condition of V.D. (aged 3 years) on readmission.
FIG. 2—Front and side views of V.D. after three months' treatment.

familial history was also referred to by Lehndorff and Mautner.

Stolte suggested the association of advanced age of the parents in some cases, and a long interval preceding the birth of the affected child. This latter is now considered to be an indication of reduced fertility.

It is also possible that we are dealing in coeliacs with an abnormal secretion of the pancreas, other than the external secretion which we consider to be normal. Another question has to be answered: Is there a general endocrine abnormality which is chiefly concerned with the pancreas? Recently Dragstedt and his co-workers have produced a factor from pancreas which they have called 'lipocaic', and which seems to have been effective in digesting fats—preventing fatty livers in depancreatized animals. Dragstedt felt that 'lipocaic' was an internal secretion of the pancreas, possibly a second hormone.

Let us go back now and consider one of the factors already brought out, that is infection. In 1925, Brown and his co-workers published the finding of a characteristic bacterial flora in the stools of coeliac patients, and dysentery was found in some cases.

EXPERIMENTAL STUDIES

Poisoning with iodo-acetic acid. Since the coeliac condition usually occurs in early infancy, and since among the principal contributing factors appear to be infection and improper feeding, we established the working theory that the coeliac syndrome might be produced in young albino rats by applying these two factors. Verzar and Laszt stated in 1936 that they were able to produce all the symptoms of coeliac syndrome in rats by poisoning them with iodo-acetic acid. Verzar found in his studies of intestinal absorption of carbohydrates that glucose and galactose were gradually absorbed; while this did not occur with other hexoses of the same molecular weight (mannose, sorbose, xylose, arabinose). These were absorbed in accordance with the law of diffusion, the former not. But the same quantity was always absorbed in a given time. Verzar postulated a special activity of the mucosa of the jejunum which is influenced by the pH of the intestinal contents. But this activity of the mucosa was inhibited by: (a) low temperature, and (b) iodo-acetic acid. It is known that iodo-acetic acid interferes with the oxidation-reduction processes connected with the resynthesis of hexose phosphoric acid during the recovery process of the muscle. If a similar transformation of glucose might occur in the cells of the intestinal mucosa, this process might be stopped by iodo-acetic acid. The constant transformation of glucose in the mucosa would maintain a high diffusion gradient between the sugar in the intestinal lumen and that in the mucosa by constantly transferring the sugar which is diffused into the mucosa cells and forms another substance.

Verzar and Laszt, studying the resorption of the fatty acids, found that glycero-phosphoric acid increased their resorption and believed that this phosphorylation process might also take place in the mucosa of the intestine. This phosphorylation process of the fatty acids was stopped by iodo-acetic acid as well as by phlorrhizin. The same inhibition of the resorption of fats took place after adrenalectomy. Wilbrandt and Lengyel studying the influence of the adrenal cortex, found that the phosphorylation process which was stopped following adrenalectomy was reversed after administration of adrenal cortex hormone, and Verzar and Laszt said that it had the same effect as riboflavin phosphate on the absorption of fats. The same authors state that poisoning with iodo-acetic acid in albino rats, when given orally, produced all the symptoms of the coeliac disease.

My colleagues, Ebbs and Stein, fed to rats the sodium salt of iodo-acetic acid with their diet. 0·1 mg. of the sodium salt of the iodo-acetic acid was mixed with the daily diet, which consisted of 10 g. approximately, but they were not able (even in repeated experiments) to observe any abnormality in these animals. They increased in weight normally and the blood count was normal.

In the next series of experiments they increased the amount of iodo-acetic acid to 10 mg. in 10 g. of diet. No effect was observed; the animals grew normally, and there was no sign of diarrhoea. They continued the experiments until the animals had reached the weight of full-grown rats and were unable to observe a single death as described by Verzar and Laszt, who regularly observed death within three weeks after the experiments had started. Even when 100 mg. of the sodium salt was given to 10 g. of diet there was only a delayed increase of weight during the first week, but the rats showed a completely normal development after this period, so that they looked like the control rats, sometimes even surpassing them in weight.

Let us discuss the reasons why they were unable to get the results obtained by Verzar and Laszt. There is first the possibility that there might be some different factors active in our diet which were not present in the European diets. Some authors refer to the fact that sulphur-containing amino acids, which are found in some cereals, prevent the effect of iodo-acetic acid, and they propose a diet with a low protein content. Such a diet, indicated by Stevenson and White, was given and it was found that there was a stunting of growth, but merely because the animals did not like the food. Besides this, the diet lacked biotin and pantothenic acid, and after some fourteen days it was observed that all the symptoms of starvation and vitamin B deficiency developed. The same effect was produced without iodo-acetic acid, another proof that the diet was deficient.

The second possibility might be that the Wistar strain used for the experiments reacted in a different manner from the strain used by Verzar and Laszt, and therefore in a new series of experiments Yale

rats were used which show a special tendency towards renal diabetes. But these rats also did not react, neither did hooded animals. In their publication Verzar and Laszt do not indicate the strain of rats they used.

The third possibility which may have played an important part in Verzar and Laszt's experiments is a chronic (more or less latent) infection in the animals they used. The coeliac-similar-syndrome they observed might have been an exacerbation of one of these infections. The most frequent infection met with in rats is bartonellosis. Martin Mayer was able to prove that this infection befalls practically every rat and is carried by the rat lice from one animal to another. Once an infection becomes active the animals die after one to two weeks, showing the symptoms of pernicious anaemia. The infection is always activated following splenectomy; the splenectomized animal succumbs within some days with the signs of pernicious anaemia. In experiments in which the blood of splenectomized rats was injected into young animals receiving iodo-active acid, an immediate stunting of growth was observed as long as the bartonella persisted in the blood. After about one week the bartonella disappeared again and the rats continued to grow in spite of feeding iodo-acetic acid. When a heavily infected strain of albino rats (not belonging to our own colony) was obtained, 10 mg. per 10 g. of the sodium salt of iodo-acetic acid was added to the diet; a loss of weight occurred and the animals showed marked diarrhoea and progressive anaemia, surviving only when vitamin B complex was given. Iodo-acetic acid given orally activates the bartonella infection in the same way as other poisons do, and it might be said that the rats used by Verzar and Laszt were more heavily infected and less resistant. It is a known fact that wild grey rats are more heavily infected with bartonella than the albinos.

Influence of infection. With these findings as a background, improper feeding and infection were then tried in a series of animals. Ebbs and Stein chose for this purpose young albino rats, twenty-one days old and with an average weight of 25 g. These animals were fed on a normal diet to which was added 20 per cent. vegetable oil with a low melting point (Mazola oil). At the same time the amount of choline was elevated to the ratio of 5 : 1,000. These rats showed in the first two weeks a partial stunting of growth, but developed later to a normal weight; the only remarkable fact was that the skin showed a greasy appearance. The latter might have been caused by the animals sitting in the food trays. The stools (although no investigation of fat content was made) showed a normal gross appearance.

The problem of producing an infection was a difficult one because a type of infection had to be chosen that would not spread all over the colony and at the same time would not produce an acute and stormy disease in the individual rat. The idea was to produce a focus of infection and for this purpose a streptococcus culture which was mixed with agar agar was chosen. The idea was that the agar agar, after becoming solid, would become a focus from which the streptococcus would spread. But it was not possible to gauge the dosage and most of the animals died after some days, and so some other method of producing the desired effect had to be tried. The rat is well known as an animal which is highly resistant to infection and, therefore, it was decided to give large doses of streptococcus toxin (0·5 ml. daily) by injection. Young rats of about 25 g. in weight were fed on the above high-fat diet. These rats showed, during the first week, stunted growth, but began to gain weight during the second week and showed, later on, a constant increase in weight although this was not as rapid as the control animals.

There was slight anaemia in both groups, but besides this no abnormalities could be detected. This picture was, however, completely reversed when iodo-acetic acid in quantities of 100 mg. per 10 g. was added to the high-fat diet. When in addition streptococcus toxin in the dosage described above was given hypodermically it resulted in a picture which resembled the coeliac syndrome in every way.

The radiographic appearances of three animals are shown in Fig. 3. The control rat (a littermate of the other two animals) was fed the high-fat diet, while the other two got 100 mg. per g. of iodo-acetic acid in their diet and besides this daily injections of streptococcus toxin. The radiographs were taken when the rats were fifty-three days old and had received the treatment for thirty-seven days. The two smallest rats developed diarrhoea, steatorrhoea, and a distended abdomen eight days after the start of the experiment. The red blood count went down to 4,500,000. On the radiograph the distended abdomen and the osteoporotic appearance of the long bones are clearly visible. The fat content of the stools went up to over 10 per cent. in this group of animals.

In another group of animals that were on the high-fat diet to which iodo-acetic acid was added, but that did not get injections of streptococcus toxin, it was noted that in spite of the rats being underweight and anaemic the fat content of the stools was not as high as in the animals who got the toxin injections, and the red blood cells did not show such a marked decrease. To be sure that the toxin by itself and not the preserving cresol solution played the important role, another group was controlled by injecting only the preserving solution, but these rats developed only the signs described in the group given high-fat diet plus iodo-acetic acid, that is, moderate anaemia and grossly retarded growth.

How can the effect of the iodo-acetic acid be explained? Why does it not produce in normal healthy rats the symptoms described by Verzar and Laszt? Ebbs and Stein were not able to find any gross pathological changes in autopsies of the animals. The liver cells were also normal and

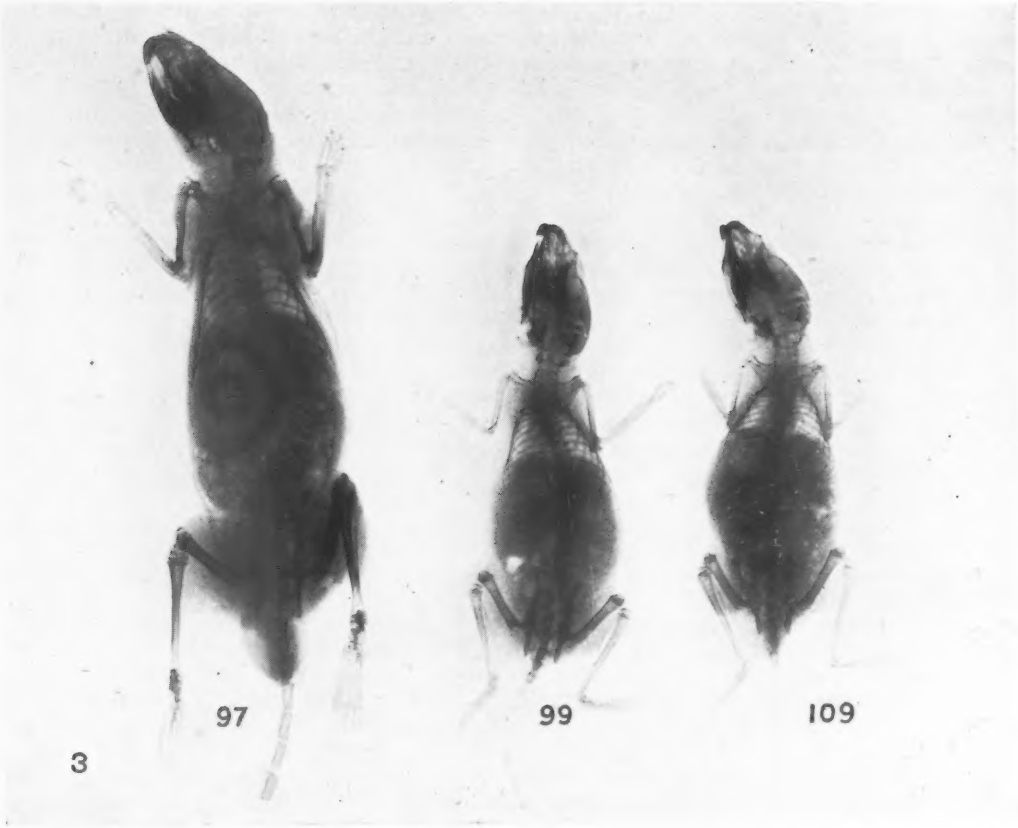


FIG. 3—Rat 97 is a control on high fat diet. Rats 99 and 109 show coeliac picture produced by giving 100 mg. per cent sodium iodoacetate and streptococcus toxin.

there were no fatty changes observed. Does the iodo-acetic acid or its sodium salt (which latter never does produce any irritating effect) activate latent bartonellosis? The explanation might be that the iodo-acetic acid has its effect only on animals whose resistance has deteriorated, and this fact might explain the production of the coeliac-similar-syndrome in young rats whose resistance was lowered as a consequence of improper feeding and streptococcus injections.

Vitamin B complex. In a series of animal experiments for which about 450 rats were used an attempt was made to find out which factor of the vitamin B complex had some therapeutic effect on animals which presented the coeliac-like-condition.

THIAMINE CHLORIDE. A group of animals fed on high-fat diet plus 100 mg. iodo-acetic acid to 10 g. of diet, and who received every day streptococcus toxin hypodermically, developed the coeliac syndrome after about one week. When 10 gamma of thiamine chloride was added to the daily diet, there was no improvement. The animals showed stunted growth, steatorrhoea, and distended abdomen. Some died after about three weeks, and others continued to gain very slowly but always looked miserable. After two months they were the weight of a normal animal of about three weeks. It has to be mentioned here that in all experiments the coeliac-similar-condition could be produced only in those rats whose initial weight was not above 25 g. Rats with the initial weight over 25 g. showed a stunted growth for about a month, later developing a gradual increase of weight.

RIBOFLAVIN, 3 mg. to 10 g. of diet, gave no results. Some rats gained very slowly, but the majority did not recover.

RIBOFLAVIN PLUS THIAMINE CHLORIDE had no effect.

NICOTINAMIDE was without any effect.

RIBOFLAVIN PHOSPHATE, 50 gamma hypodermically daily, had no effect; indeed the rats died almost earlier as compared with other groups and the diarrhoea was even more accentuated in these animals. (It might be possible that the acid as such acted as a poison.) Riboflavin phosphate fed with the diet (100 gamma daily) had no effect either. These experiments did not confirm Verzar and Laszt's postulations which claim that 'Flavinphosphoraeure' is the effective substance in the re-establishment of the impaired phosphorylation process caused by iodo-acetic acid poisoning.

BREWER'S YEAST. When 250 mg. Brewer's yeast was added to the diet containing 100 mg. of iodo-acetic acid per 10 g. and 20 per cent. of fat, plus streptococcus injections, there was an immediate gain of weight in the animals (Fig. 4). The fat content of the stools went down from 10 to about 7 per cent., and the red cell count increased from 4,500,000 to 6,500,000 per c.mm. of blood in two weeks. One month after the introduction of Brewer's yeast the animals regained the weight and could not be distinguished from normal rats. How the effect produced by Brewer's yeast may be explained is difficult to say. When riboflavin phosphate is the

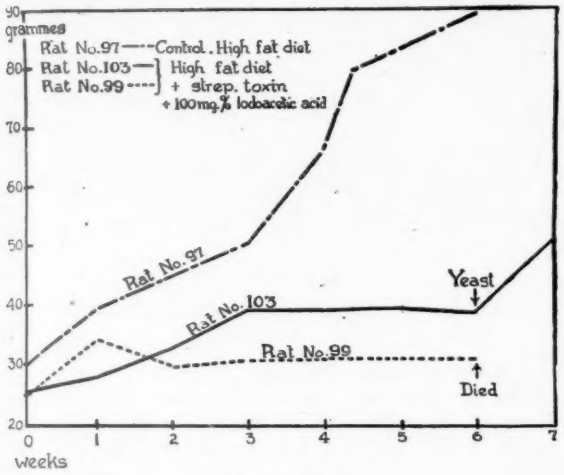


FIG. 4.

active substance, why does it not act in its pure form, but only within the vitamin B complex? Are there other factors belonging to the vitamin B group which are responsible for this activity? Should the effect of Brewer's yeast be based on the fact that the amino acids contained therein prevent the effect of the iodo-acetic acid? To find an answer a control group was fed amino acids 'Amigen' in the same amount as Brewer's yeast, but this did not show any protective effect. The animals died within a few days while the controls fed Brewer's yeast survived and increased in weight.

Adrenal cortex. A study of the effect of adrenal cortex hormone was carried out. To be sure of the poisonous effect of iodo-acetic acid, the sodium salt was injected every second day into a group of nine animals in doses of 0·1 mg. Five of them died within one week and the remaining four showed the typical symptoms described before. Some of these were given a daily dose of 0·5 ml. of adrenal cortex (15 dog units) hypodermically. The animals on adrenal cortex showed a slow increase in weight, the red cell count was 5,700,000 per c.mm. of blood while the red cell count in the animal which did not receive adrenal cortex hormone was 4,700,000. The fat content in the stools was 10·8 per cent. in the animal which did not receive adrenal cortex and 8·4 per cent. in the other animal.

Folic acid was given to a group of coeliac rats, but this had little or no effect upon the condition of the animals.

A question concerning these experiments is: Can the coeliac symptoms in albino rats, produced by the above-described methods, be prevented? The answer is, if the rats are fed Brewer's yeast, they do not show any of the signs. When Brewer's yeast, 250 mg. daily, is given at the same time as the high-fat diet, the feeding of iodo-acetic acid, and/or the injection of streptococcus toxin, the rats develop normally and there is no sign of any of the coeliac changes.

Theories of the pathogenesis of coeliac disease. In 1932 Parsons' work in the Children's Hospital in Birmingham showed that although the faecal fat is not identical with the food fat, yet it depends upon the food fat and shows parallel variations. The theory that coeliac disease has an infectious origin has been worked upon by a number of investigators. In 1925 in our own clinic we found characteristic bacterial flora. In these cases it suggested a bacterial origin. Parsons investigated the bile in coeliac children and showed it to be similar to that in the normal child. In the important review by Parsons in 1932 he found that no one of the theories of etiology which were suggested could be considered adequate. He concluded that although up to the present no changes have been found in the intestinal secretion, the probable explanation of the coeliac disease lies in a change of physiochemical nature in the absorptive mechanism of the intestine. More recent studies lead to the same conclusion but the nature and cause of this physical, chemical change has yet to be determined.

As a result of numerous experiments in his Department, Frazer in 1947, in an interesting review of the 'Etiology of Steatorrhoea', has described the phases of fat absorption as divided into the intra-luminar phase in which the fat is finally dispersed into a number of small particles, and the subsequent absorption through the cell wall lining the intestines. He has shown that fatty acids, monoglyceride, and bile salts must be present in order to get the maximum emulsification of the fat. This preparatory emulsification of the fat would be lost in conditions in which pancreatic enzymes were lost, that is in fibrocystic disease of the pancreas. He has suggested that fat is absorbed through the intestinal cells in the form of fatty acid or in small particles of fat, in which case the fatty acids reach the liver via the portal vein and the particles of fat reach the thoracic duct and then go into the blood stream.

Whether deficiency signs and symptoms in this condition are primary or secondary is still debatable. Peters in 1930 suggested that the B complex might be associated with fat metabolism. In 1942 May and his co-workers revived this view and thought that coeliac disease might be due to lack of specific food factor. They produced evidence of clinical improvement in patients treated with crude liver

extract. Folic acid therapy has been reported as giving help in some cases, but the results have not been uniform.

Gastro-intestinal allergy seems to have been associated in some cases of coeliac syndrome, and there are numerous reports suggesting this to be one of the causes. In 1938 in an important pathological investigation, Andersen separated coeliac disease from cystic fibrosis of the pancreas, on the basis of the presence or absence of pancreatic enzymes in the duodenal juice, and the presence or absence of the fibrotic changes of the pancreas at autopsy. Following this, May and his co-workers have done extensive work on faulty absorption in coeliacs and have pointed out that motility in the gastro-intestinal tract is reduced in coeliac disease. This impaired mechanical function, they claim, explains the defective absorption of carbohydrates. They also pointed out clumping of barium meal in the small intestine. The vitamin A absorption test was low in coeliac children, but tended to return to normal and the patient recovered. May, McCreary, and Blackfan in 1942, stated that it is now generally accepted that the basic fault in coeliac disease is defective absorption from the intestine, particularly fat and carbohydrate.

Andersen in 1947, in a discussion with relation to coeliac disease, points out that the lipase content of the duodenal juice is normal in the coeliac child, and according to her, this disease is an expression of a multiple deficiency state, when it is fully developed. This condition probably arises only in children with an underlying constitutional defect. Andersen pointed to the high familial incidence of the disease and to the incidence of starch intolerance in the siblings of coeliac children.

The majority of evidence to date points to a defect in the absorptive power of the intestine for fats and carbohydrates. The reason for this deficient absorption is still not known; infection, vitamin deficiency, allergy, constitutional factors, or a combination of any of these are all possibilities which have been put forward.

Summary

It must be apparent from the studies which we have made that very little has actually been added to our knowledge of this disease. However, our studies have served to emphasize again the fact that much of the knowledge of this disease, as recorded by the earliest writers on the subject, is being proven again. Particularly one is impressed by the presence of infection at the onset of this disease and by improper feeding during infancy and childhood.

The preliminary results of the dental survey indicate that the well-known clinical observation that children who have suffered from coeliac disease and have had proper dietary control are blessed with better than average teeth, is probably true.

The genetic investigation has thrown some light on the probable relation of coeliac disease to diabetes, and a possible pancreatic dysfunction of some type.

In experimental studies with animals the factor of infection has been emphasized and would appear to be a very important one.

The relation of vitamin B complex to the prevention and relief of the coeliac syndrome deserves further investigation.

Finally the cause of this condition can apparently be solved only by continued, co-operative effort in numerous branches of medical science.

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THE EFFECT OF TOXAEMIA OF PREGNANCY UPON THE FOETUS AND NEWBORN CHILD*

BY

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There exists a widespread impression that the infants of mothers suffering from toxaemia of pregnancy have a less than normal prospect of surviving the newborn period, and that if they survive their progress is less satisfactory than that of infants born of healthy women. There is also a tendency to attribute, somewhat vaguely, post-natal symptoms in these infants to the maternal toxaemia. The rather scanty literature is not very informative with regard to the prospects of survival of liveborn infants of toxaemic mothers, though numerous authors have emphasized the increased likelihood of foetal death or premature birth. Tunis (1928) considered that direct transmission of eclampsia was unimportant as a cause of foetal death, and concluded that prematurity was the major factor, associated with a greater risk of intra-uterine asphyxia. Strauch (1939) also commented on the high foetal mortality, which he ascribed in part to prematurity, in part to placental damage, and in part to the asphyxia produced by the maternal convulsions. He argued in favour of the occurrence of neonatal eclampsia, quoting previous authors in support of this. Peckham (1933) analysed the foetal mortality and found it to be directly proportional to the severity and duration of the toxaemia, and inversely proportional to the duration of pregnancy at the time of onset of the toxaemia. He included nephritic cases and found that the mortality was much higher amongst the infants of nephritics than in those of non-nephritics.

Tyson and Bowman (1931) studied twenty-nine cases of eclampsia and forty-nine of pre-eclamptic toxaemia, and found the foetal mortality in each group to be higher than the average, and in the former higher than in the latter. They ascribed the high mortality solely to premature birth resulting from the toxaemia. In a follow-up of the survivors, over periods varying from one month to one year, they found no evidence of any remote ill-effects of the maternal toxaemia.

Tunis (1928) and Von Reuss (1916), whom he quotes, also carried out a follow-up of their cases, and found no evidence of any ill effects. Pilcz (1900), on the other hand, quoted by Tunis, gave a mortality rate of 59 per cent. among 350 children of eclamptic mothers, but Tunis points out that he drew his material from an institution which had in any case a high death rate.

Ludlow (1933) assessed the incidence of stillbirth and neonatal death, and the progress of the survivors, among 148 infants of toxaemic mothers, and made a comparison with infants of healthy mothers. He concluded that full-term infants of toxaemic mothers have a higher incidence of stillbirth and neonatal death, a lower average birthweight, and a less satisfactory gain in weight while in hospital, than those of healthy mothers; that eclampsia has no worse influence than pre-eclamptic toxaemia, but that nephritis has a worse effect than either. Premature infants, however, showed a wholly different comparison; those born of toxaemic mothers had a lower neonatal death rate and a better average weight-gain than those of healthy mothers, and the infants of nephritic mothers fared better still. Necropsies were performed on a number of the infants dying in the neonatal period; four are said to have shown evidence of toxaemia, this evidence being defined as autolysis, placental infarction, asphyxia, and maceration.

Drillien (1947a, b, c) made a study of prematurity, stillbirth, and neonatal death, and concluded that although toxaemia has a significant and marked effect in causing premature birth it has no adverse effect on the foetus and premature infant (as judged by survival rates) other than that on the birthweight. She found that the survival rates among premature infants were slightly higher for the infants of toxaemic than for those of healthy women. She suggests that toxaemia might be an important factor in the production of intra-uterine death, with or without demonstrable asphyxia.

Peckham (1933) states that breast feeding is less successful in toxaemic than in healthy mothers, but he gives no evidence in support of this view.

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Ludlow (1933) found that the milk of toxaemic mothers had no apparent ill effects upon their infants.

Rucker and Connell (1924), in the course of investigating the normal blood pressure in the newborn, concluded on the basis of five cases that ' toxic conditions of the mother seem to have some influence on the blood pressure of the child, which is more marked the first day of life.' Browne and Dodds (1936) made daily readings of the systolic blood pressure of three infants whose mothers had hypertension before delivery, and found them not significantly higher than those of six normal controls.

Smith (1945) quotes Salmi as stating that albuminuria occurs more often in the infants of albuminuric mothers than in those of healthy mothers.

Present Investigation

In view of the somewhat conflicting evidence, the present investigation was undertaken primarily to determine whether toxaemia of pregnancy could be shown to have any effects on liveborn infants, and particularly on those surviving the neonatal period. It was accepted that maternal toxaemia was a cause of prematurity, and a comparison was made between the progress of premature infants of toxaemic and non-toxaemic mothers, and similarly between full-term infants of toxaemic and non-toxaemic mothers. Information was also added with regard to stillbirths and neonatal deaths.

Clinical material. All the infants studied were born in the Simpson Memorial Maternity Pavilion, Royal Infirmary, Edinburgh, during the years 1942-47, with the exception of a small number of premature babies admitted within a few hours of birth from the hospital district during 1946. In the case of stillbirths and neonatal deaths, information was obtained from mothers' and infants' case notes and post-mortem reports and not from personal observation. The cases were as far as possible consecutive, but in some instances cases had to be excluded on account of incomplete or missing maternal case records; as far as could be determined, this did not materially affect the sample.

The infants included in the premature series were all born during 1946, though not all were seen personally. In the series of mature surviving infants, all were observed personally during 1947. Those in the toxaemic group were consecutive live-births over a period of approximately six months; the controls were obtained by random sampling of full-term infants in the same nurseries at the same time.

Definition of toxaemia. The term ' toxaemia of pregnancy ' has been used throughout to include eclampsia, pre-eclampsia, and hypertension, whether arising for the first time during pregnancy or existing previously. Any case diagnosed as nephritis has been excluded; the diagnosis of nephritis rested on a history or on signs of renal damage before the twenty-fourth week of pregnancy. Three cases were thus excluded in each of the stillbirth and neonatal death series, and one in the series of mature surviving infants: cases of all grades of severity have been included, and an arbitrary definition of severity has been adopted which classified as ' severe ' all cases reaching a diastolic blood pressure of 130 mm. or more, and cases with a diastolic pressure of 110 mm. if they had also a well marked albuminuria.

Surviving Full-Term Infants

One hundred and twenty full-term liveborn infants of toxaemic mothers were compared with the same number of controls born to non-toxaemic mothers. Comparison was made of the birthweight, initial loss of weight, progress as judged by weight-gain, lethargy, liability to infection and other morbid conditions, oedema, albuminuria, and blood pressure. The maternal histories and lactation in the two groups were also compared.

Maternal history. In the toxaemic group, the toxaemia (including eclampsia) was classified as severe in twenty-one instances and mild or moderate in ninety-nine. The duration of toxaemia was as follows:

1 week or less	0
1 to 4 weeks	24
4 to 8 weeks	54
More than 8 weeks	22
Uncertain	20

A comparison of other features of the maternal histories is shown in table 1.

TABLE 1
COMPARISON OF MATERNAL HISTORIES

	Toxaemic	Control
Primiparae without previous abortion	76	77
Primiparae plus previous abortions	8	10
Multiparae without previous abortions	28	28
Multiparae plus previous abortions	8	5
Twin (toxaemic : 9 pairs, 1 single)	19	0
Previous toxaemia	15	1
Previous stillbirth	7	5
Previous neonatal death	2	2
Ante-partum haemorrhage (without placenta praevia)	1	3
Ante-partum haemorrhage (with placenta praevia)	0	2
Placental infarction: slight	21	6
Placental infarction: marked	12	6
Spontaneous vertex delivery	71	103
Caesarean section	13	9
Forceps delivery	28	5
Breech delivery	8	3

Birthweight. The distribution of birthweights of all the infants in the two groups is shown in fig. 1, 5½ lb. (2,500 g.) being taken as the accepted standard of maturity. The mean birthweight in the toxaemic group was 7 lb. 3 oz., and that in the control group 7 lb. 6½ oz.

Initial weight loss. Fig. 2 shows the relation between birthweight and initial weight loss. The initial loss tends, as might be expected, to vary with birthweight, but more noticeably so above a birthweight of 7 lb. 8 oz. The curves for toxaemics and controls are in general similar. In the toxaemic

group, the mean initial loss was 9·8 oz. with a range of 4 to 12 oz.; in the control group it was 9·3 oz. with a range of 4 to 17 oz.

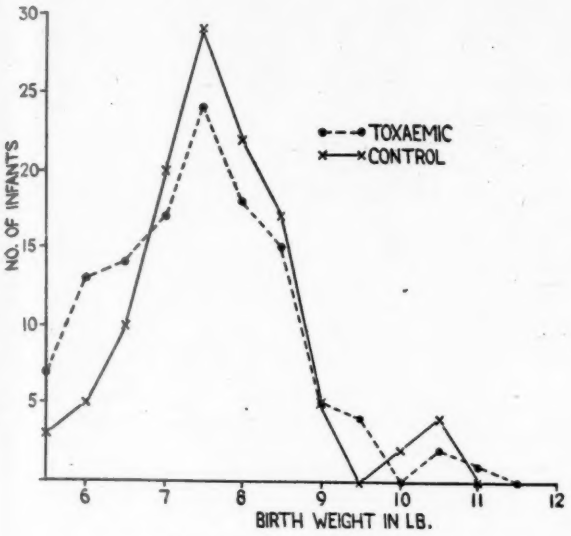

FIG. 1.—Distribution of birthweights of full-term infants of toxaemic mothers and controls.

Weight gain. The infants in the toxaemic and control groups were each divided into fifteen sub-groups on the basis of birthweight (using a weight range of 4 oz. in the case of the smaller infants and 8 or 12 oz. in the case of the heavier infants). The mean weight curves of the toxaemic and control infants in each sub-group were then compared up to the eighth day of life. Detailed figures are given elsewhere (Brash, 1948). It was found that in three instances the gain in weight of the toxaemic infants was inferior to the controls, in three it was superior, and in the remaining nine instances there was no significant difference. It is concluded that this comparison does not furnish any evidence of the full-term infants of toxaemic mothers being at a disadvantage as regards gain in weight during the first eight days of life when compared with non-toxaemic controls of similar birthweight.

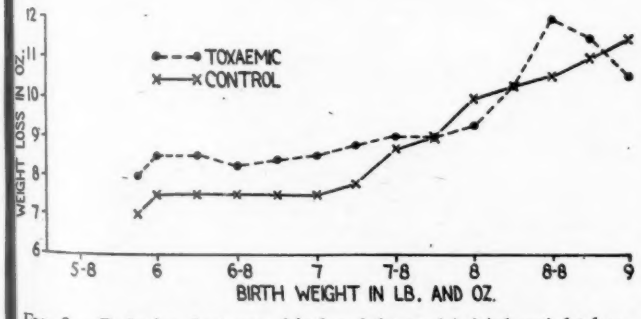

FIG. 2.—Relation between birthweight and initial weight loss.

Lethargy and shock. Abnormal lethargy for some days after birth is shown principally by slowness in feeding, whether at the breast or from a bottle. Of the infants of toxaemic mothers, eleven were classified as lethargic, of the controls only one. Of the eleven, the mothers of three had had their labour induced and had been heavily sedated before an abnormal delivery, six more had an induction of labour, one having also a difficult natural delivery, one had a Caesarean section, and one had a moderate amount of sedative before delivery. The mother of the one control infant had also been given a moderate amount of sedative before delivery.

Evidence of shock at delivery was observed in twenty-one of the toxaemic group (three also showing lethargy for several days after birth), and in sixteen in the control group.

Incidence of infection. Nine infants in the toxaemic and eight in the control group acquired infections during the neonatal period. In the toxaemic group, three infants had mild attacks of gastro-enteritis, two in the first week, of whom one had nasopharyngitis as well. One developed dacryocystitis in the first week, and two had thrush; one of the latter had pneumonia in the fourth week. One child developed septic spots in the second week, and another a boil in the third week. There was one case of undiagnosed fever and loss of weight in the second week, with quick recovery.

In the control group there were five cases of septic spots and two of thrush, all in the first week; one infant developed a septic hand in the second week.

Other morbid conditions. Five infants in each group displayed some morbid condition, of which details follow.

A. TOXAEMIC GROUP. One infant had two convulsions in the first twenty-four hours; this child was delivered spontaneously of a severely toxaemic mother after an induction of labour; there were no other abnormal features, and progress after the first twenty-four hours was uneventful.

One was very lethargic for four days and oedematous for six; there was a single colour change on the second day, and deep physiological jaundice from the third to the eleventh day; there was no gain in weight until the third week, but progress from then on was satisfactory; the mother was suffering from moderate toxaemia, and delivery was spontaneous after an induction of labour.

Two ' murmured ' during their first twenty-four hours; each was delivered spontaneously after an induction of labour; the mother of one had severe toxaemia, and of the other moderate hypertension.

B. CONTROL GROUP. One infant failed to gain any weight while in hospital, in spite of apparently adequate test-feeds. One lost weight for the first ten days; this infant was artificially fed because the mother had open pulmonary tuberculosis; he presented no abnormal sign other than the loss of weight, and made satisfactory progress after the

tenth day. Two developed dehydration fever. One had a feeble cry and shallow respirations for the first twenty-four hours, but did well thereafter; this infant had undergone breech delivery.

Oedema. Hallum (1941) states that oedema of the newborn, although common in premature infants, is rare in those born at term. Of 211 cases of oedema occurring in premature infants (from the records of the Birmingham City Maternity Home), thirty-six had a history of maternal toxaemia, but among her own cases six of the mothers were toxaemic.

All the infants in the present series were examined for the presence of oedema. This was found in none of the control group, whereas in the toxaemic group two showed slight oedema of the legs, lasting one and six days respectively; two showed moderate oedema of the legs, lasting six and twelve days respectively. Of the mothers of these infants, one of each pair was suffering from mild and the other from severe toxaemia.

Albuminuria. Young et al. (1941) quote Von Reuss to the effect that albumin was found in 96 per cent. of infants during the first four days of life, and Smith (1945) states that albuminuria is found in the majority of newborn infants, particularly prematures, from the second to the fifth day.

Urine specimens were obtained on the third day from ten infants of the toxaemic group and from twenty-five controls. Albumin was found in only one (10 per cent.) of the former, and in ten (40 per cent.) of the controls.

Blood pressure. Blood pressure readings in small infants are difficult to standardize and record accurately. It is necessary to have the infant at rest; auscultation of the brachial artery is not practicable by the ordinary methods, and palpation of the radial pulse is often difficult. The width of the cuff used introduces a further variable factor.

Rucker and Connell (1924), using an oscillometer, found the average systolic pressure at birth to be 55 mm. Hg, the average diastolic to be 40 mm., and the pressure to be proportional to the total length of the infant. They do not state the width of the cuff which they used. Woodbury et al. (1938) measured the blood pressure at birth with a cannula in the umbilical artery, and found that the readings corresponded with those obtained by palpation at the wrist when a 2·5 cm. cuff was used; they concluded that the usual 5 cm. cuff gives too low readings. Day (1939) investigated the effect of cuff-width in children and adults; he found that widening the cuff lowers the reading until a certain point is reached, after which the reading remains constant, and concluded that as wide a cuff as possible is the most reliable and should be used. Smith (1945), quoting Woodbury et al., states that a 2·5 cm. cuff must be used, and that the systolic pressure is 70 to 80 mm. Hg at birth and 95-100 mm. Hg on the tenth day.

In the present investigation a 6 cm. cuff was used, and the systolic pressure was read by palpation of the radial artery at the wrist. Estimation of the diastolic pressure was not attempted. Difficulty was often encountered in feeling the radial pulse, but in only four cases was it given up as impossible. All readings were made with the infant quiet, but very few during sleep.

In fifty cases in the toxaemic and a hundred cases in the control group a reading was made on the first and on the eighth day of life. In a further twenty cases in each group daily readings were made for the first eight days.

Fig. 3 shows the distribution of all the readings on the first and on the eighth day. It will be seen that the scatter is similar in the two groups, with peaks between 40 and 45 mm. Hg on the first day, and between 70 and 85 mm. Hg on the eighth. The average systolic pressure on the first day was 48·3 in the toxaemic group, with a range of 25 to 80, and 55·4 in the control, with a range of 35 to 90. On the eighth day it was 74 in the toxaemic group, with a range of 45 to 95, and 73·9 in the control, with a range of 45 to 100. Five infants of severely toxaemic mothers gave average readings of 46·2 on the first day, and 73 on the eighth.

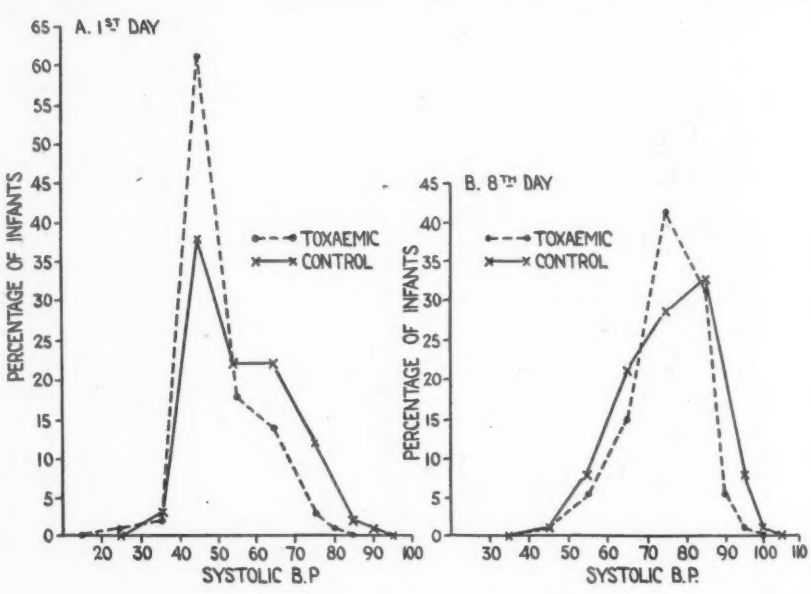

FIG. 3.—Percentage distribution of blood pressures on first and eighth days.

Table 2 gives the individual daily readings made on twenty 'toxaemic' and twenty control infants. Though there was in all cases a rise in pressure by the eighth day, in no instance was it a steady one, and nearly all the infants showed a temporary fall at some point. Several infants in the toxaemic group showed an initial fall in pressure, but so also did several in the control group, and there is no form of curve in the former which is not paralleled in the latter.

TABLE 2

DAILY BLOOD-PRESSURE READINGS IN TOXAEMIC AND CONTROL GROUPS

	Case	Day of life 1	2	3	4	5	6	7	8
A. Toxaemic	1	50	50	45	85	65	75	75	70
	2	55	60	55	65	60	60	85	70
	3	40	60	65	60	65	60	70	65
	4	45	65	70	75	60	70	85	85
	5	50	45	65	85	85	85	85	100
	6 (twins)	35	50	60	60	50	65	65	70
	7 (twins)	35	40	50	45	70	65	40	55
	8	65	85	70	80	75	75	60	85
	9	40	45	70	50	75	65	80	80
	10	45	65	65	65	65	65	75	75
	11 (twins)	45	45	50	65	70	65	75	80
	12 (twins)	45	55	65	80	60	60	85	85
	13	50	45	60	65	60	75	70	70
	14	55	45	50	65	60	85	95	70
	15	45	60	65	70	80	75	65	75
	16	40	60	60	80	80	80	85	75
	17	60	45	90	60	95	75	75	85
	18	60	55	75	90	70	70	75	80
	19	65	70	65	75	60	65	70	70
	20	65	65	75	85	70	95	70	90
B. Controls	1	55	50	45	65	65	65	70	75
	2	30	60	55	50	55	65	55	65
	3	45	65	65	65	75	65	80	70
	4	45	70	70	70	45	65	60	60
	5	45	70	65	75	75	75	70	85
	6	40	65	65	65	80	75	100	95
	7	45	55	65	65	70	80	85	75
	8	55	65	60	75	85	85	85	85
	9	45	45	45	65	85	85	105	85
	10	40	45	55	75	55	60	55	65
	11	55	45	45	55	65	75	75	85
	12	45	65	65	60	65	65	70	65
	13	55	65	50	75	65	85	75	85
	14	60	65	65	80	75	95	90	80
	15	45	65	65	65	75	80	85	75
	16	45	95	60	75	65	60	85	75
	17	65	65	65	70	75	65	70	80
	18	50	50	60	70	80	75	75	80
	19	40	60	55	55	65	65	70	75
	20	50	50	50	55	95	80	85	85

Twelve infants in the control group, in whom readings were taken on the first and eighth day only, had a lower pressure on the eighth day than on the first.

The above findings indicate that the systolic blood pressure is similar during the first eight days of life in the infants of toxaemic mothers and in controls. In both groups there is a tendency for the blood pressure to rise during the first eight days, and although the rise is not necessarily steady or consistent, the distribution of readings at the beginning and end of the period is similar in both groups. Fallacies in the technique of recording pressures would affect both groups equally, and the results are therefore comparable.

Premature Births

The incidence of stillbirth and neonatal death in toxaemic and in non-toxaemic pregnancy terminating prematurely was calculated on the basis of all the premature births occurring in the hospital over a three-year period. For some of the figures on which these calculations are based I am indebted to Dr. C. M. Drillien.

	Toxaemic	Control
Stillbirth	19 per cent.	23·9 per cent.
Neonatal death	20·8 per cent.	27·2 per cent.

The progress of the surviving premature infants has been compared by estimating the rate of gain in weight of all such infants over 2½ lb. treated during one year, whether born in the hospital or admitted from the hospital district on account of prematurity within a few hours of birth. The infants were divided into sub-groups on the basis of birthweight, and the average weight of the sub-group at weekly intervals was calculated; toxaemic and control groups were then compared in each instance.

It was found that in four of the nine sub-groups the progress of the 'toxaemic' prematures was slightly superior to that of the controls, in two it was slightly inferior, and in three instances the curves showed no significant difference. It is concluded that the progress of prematurely born infants, over periods of four to twelve weeks in hospital, was at least as good in the case of the infants of toxaemic mothers as in the case of infants where prematurity was due to some other cause. (The detailed figures are given elsewhere, Brash, 1948.)

Incidence of prematurity. Fig. 4 shows the distribution of birthweights in two thousand consecutive live births, divided into toxaemic and

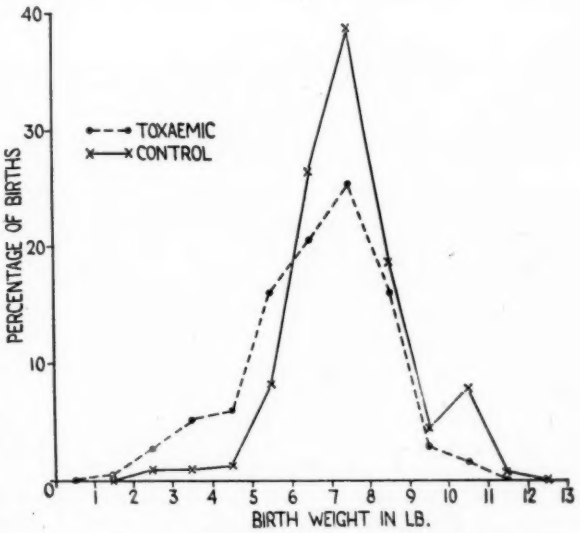

FIG. 4.—Percentage distribution of birthweights in two thousand consecutive live births.

non-toxaemic groups, the number in each weight-range being expressed as a percentage of the total births to toxaemic and non-toxaemic mothers respectively. The incidence of prematurity is seen to be significantly greater in the toxaemic than in the non-toxaemic group.

Stillbirths

The incidence of stillbirth in toxaemic and in non-toxaemic pregnancy was calculated on the basis of all the births occurring in the hospital over a three-year period. The incidence of stillbirth in 756 pregnancies complicated by toxaemia was 10·7 per cent.; that in 8,313 pregnancies not so complicated was 3·9 per cent.

In each of the two hundred cases in this series (one hundred toxaemic, one hundred non-toxaemic) a study was made of the antenatal history, the labour, and the delivery, together with a post-mortem report on the infant where available. The maternal history was considered in each case, and the cases showing abnormal factors which might cause foetal death were grouped together. The results are shown in table 3.

TABLE 3
ANTENATAL HISTORY, LABOUR, AND DELIVERY

	Toxaemic	Control
Abnormal labour and/or delivery (including intra-partum eclampsia)	49	58
Foetal abnormalities (sufficient to account for death and not included above)	4	12
Ante-partum haemorrhage (not included above)	18	8
Placental infarction (not included above)	16	4
Various	2	4
Unaccountable	11	14

Necropsies were performed on thirty-eight infants in the toxaemic group and thirty-five in the control. Table 4 shows the causes of death reported in these cases.

TABLE 4
CAUSES OF DEATH

	Toxaemic	Control
Asphyxia	23	18
Intra-cranial haemorrhage	8	8
Not determined	7	9

In no case in either group were toxic changes found in the liver or kidneys.

Neonatal Deaths

The incidence of neonatal death in toxaemic and in non-toxaemic pregnancy was calculated on the basis of all the births occurring in the hospital over a three-year period. The incidence of neonatal death in 756 pregnancies complicated by toxaemia was 5·2 per cent.; that in 8,313 pregnancies not so complicated was 2·9 per cent. (There is a possible source of error in this calculation, in that deaths occurring after discharge from hospital but within the neonatal period are not included; the number of these is certainly very small.)

In each of the two hundred cases in this series a study was made of the antenatal history, the labour, and the delivery, the clinical record of the infant, and the post-mortem report where available.

Fig. 5 shows the age at death by means of a cumulative curve showing the number dead on each

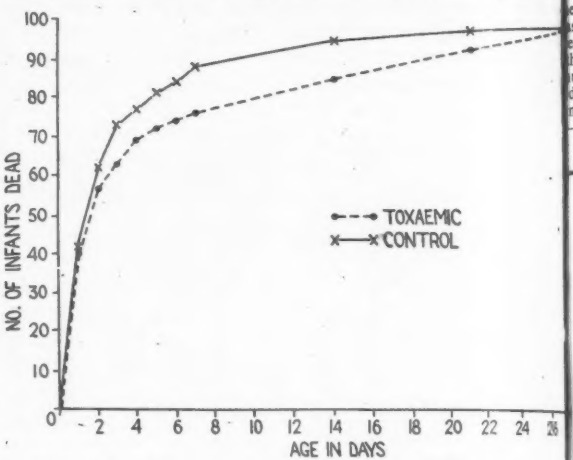

FIG. 5.—Cumulative curve to show age at death.

day of the first week, and at the end of each subsequent week of the neonatal period. It will be seen that the vast majority of the deaths occurred within the first few days of life, and that the curves are similar for the toxaemic and control groups.

In analysing the causes of the deaths, those occurring within the first five days were considered as one group, and those occurring later as another, because the majority of deaths in the first four or five days may justly be attributed to obstetric factors, while those occurring after the fourth or fifth day are commonly due to factors arising after birth.

The infants were further subdivided into groups according to birthweight, the term 'pre-viable' being applied arbitrarily to those weighing less than $2\frac{3}{4}$ lb. (1,250 g.) and 'premature' to those weighing from $2\frac{3}{4}$ lb. to $5\frac{1}{2}$ lb. (1,250 g. to 2,500 g.).

Necropsies were performed on eighty-nine infants in the toxaemic and ninety-two in the control group. The findings are summarized in tables 5 and 6, the term asphyxia being used to include post-asphyxial pneumonia.

TABLE 5
DEATHS WITHIN THE FIRST FIVE DAYS

	Pre-viable		Premature		Mature		Total	
	Toxaemic	Control	Toxaemic	Control	Toxaemic	Control	Toxaemic	Control
Asphyxia	13	27	23	30	7	8	43	65
Intracranial haemorrhage	3	1	6	–	2	1	11	2
Other causes	6	3	5	3	2	6	13	12
Cause not determined	–	–	2	1	1	1	3	2
Total	22	31	36	34	12	16	70	81

TABLE 6

DEATHS AFTER THE FIFTH DAY

	Pre-viable		Premature		Mature		Total	
	Tox-aemic	Con-trol	Tox-aemic	Con-trol	Tox-aemic	Con-trol	Tox-aemic	Con-trol
eumonia	3	–	10	9	2	3	15	12
astro-enteritis	–	–	7	1	2	–	9	1
ther causes	–	2	2	–	2	3	4	5
use not deter-mined	–	–	2	–	–	1	2	1
Total	3	2	21	10	6	7	30	19

In the group dying within five days there appears to be a relative preponderance of intracranial haemorrhage in the premature infants of toxaemic mothers. The criterion adopted for assessing intracranial haemorrhage as the cause of death was severe haemorrhage with no more than slight evidence of asphyxia. It is nevertheless impossible to be certain that even severe haemorrhage was not due to asphyxia, and that most of these cases should not therefore be included under the latter heading.

Asphyxia without a recognizable cause, such as abnormality of labour or delivery, ante-partum haemorrhage, or placental infarction, was found in nine cases in the toxaemic and twenty-one in the control group, of which eight in the toxaemic and eleven in the control group were below 2¾ lb. at birth.

The cause of death remained undetermined in five cases in the toxaemic group and three in the control. Of those in the toxaemic group, one was a mature infant who had been delivered abnormally and who died before the fifth day; the other four were premature infants whose deaths could not be accounted for clinically, and necropsies carried out on two were inconclusive. Of those in the control group, one was a premature infant dying within the first two days, whose mother had ante-partum haemorrhage and whose placenta was infarcted; one was a mature infant dying within the first few days who had been delivered abnormally and who showed clinical signs of intracranial haemorrhage; the third was a mature infant dying after the fifth day on whom necropsy was inconclusive.

In this series toxic or degenerative changes in the liver and kidneys were found at necropsy as follows:

TOXAEMIC. Two infants showed toxic changes in both liver and kidneys; both were more than five days old and died of staphylococcal pneumonia. Two showed hydropic degeneration of the liver; both were under five days old: one was asphyxiated, and the other had severe intracranial haemorrhage and also pulmonary and renal haemorrhage.

CONTROL. One infant showed toxic changes in both liver and kidneys; this infant was under five days old and was thought, but not proved, to have streptococcal septicaemia. Ten showed fatty degeneration of the liver; eight of these were under five days and were asphyxiated; two were over five days and had pneumonia. One showed toxic changes in the kidneys only; this child was under five days and was asphyxiated.

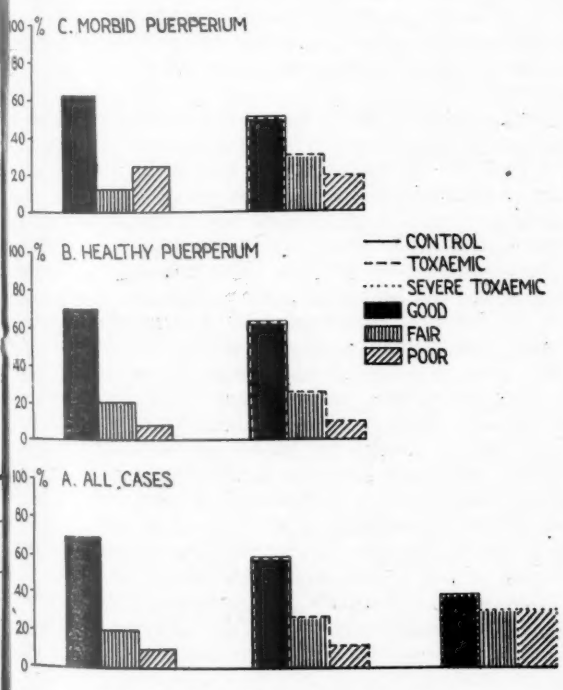

FIG. 6.—Relationship of lactation (good, fair, or poor) to toxaemia and type of puerperium (healthy or morbid).

Lactation

The adequacy of maternal lactation was assessed in the series of one hundred and twenty full-term infants of toxaemic mothers and the corresponding series of one hundred and twenty non-toxaemic controls. As daily test-weighing of all infants at all feeds was impracticable, the assessment (which is admittedly only a rough index of lactation) was based on satisfactory gain in weight of the infant in the first instance. Where the gain in weight was not fully satisfactory, test-feeds showing an average of 2 oz. or more per feed at the end of the first week were regarded as evidence of good lactation. Lactation was graded as poor if test-feeds were consistently under 1½ oz. Intermediate cases were classified as fair.

The lactation of toxaemic and non-toxaemic women was compared on this basis, and the groups again compared after dividing into those with a healthy and those with a morbid puerperium. The results are shown in table 7.

TABLE 7
LACTATION OF TOXAEMIC WOMEN AND CONTROLS, EXPRESSED PER CENT.

Lactation	All cases		Healthy puerperium		Morbid puerperium	
	Toxaemic	Control	Toxaemic	Control	Toxaemic	Control
Good ..	59	70	63	70	50	62·5
Fair ..	27	20	26	21	31	12·5
Poor ..	14	10	11	9	19	25

In fig. 6 the relationship of lactation to toxaemia is shown graphically, and the cases of severe toxaemia are also shown separately. It is clear that the toxaemic women lactated less well than the controls, and that those with severe toxaemia lactated less well than those where toxaemia was mild or moderate. Puerperal morbidity, as would be expected, is shown to have an adverse effect on lactation in both toxaemic women and controls.

Whilst the finding that lactation was less good in toxaemic women than in controls confirms Peckham's (1933) opinion, it is possibly related to the fact that the number of abnormal labours and deliveries, with the consequent administration of sedatives and anaesthetics, was higher in the toxaemic than in the control group. Ludlow (1933) found that there were no ill effects attributable to the breast milk of toxaemic mothers, and the present investigation confirms this view.

Discussion

The stillbirth rate for mature infants is considerably higher in the presence of the toxaemia of pregnancy than its absence, and the question arises whether this is due directly to a lethal effect of the maternal condition upon the foetus; that is, to some substance circulating in the maternal blood and passing the placental barrier to reach the foetal circulation, or to an increased incidence of the same factors which cause stillbirth in the absence of toxaemia.

In this series the findings in the limited number of necropsies carried out were similar in the toxaemic and in the control groups, asphyxia being the cause of death in the majority and intra-cranial haemorrhage in a smaller number. In a fair proportion the cause of death could not be determined at necropsy, but as the number was greater in the control than in the toxaemic group a hypothetical toxin cannot be held responsible. In no case were toxic changes, such as have been described by Esch and other authors, found to be present. The number submitted to necropsy in this particular series was small, but Dr. A. R. Macgregor in a very large number of necropsies has never seen such changes (personal communication). Autolysis, placental infarction, asphyxia, and maceration, all found frequently in the offspring of non-toxaemic mothers, do not merit the description 'evidence of toxaemia' given them by Ludlow.

The cases examined post mortem being a minority, an attempt was made to assess the cause of stillbirth from the obstetric history. Conditions which may lead to foetal asphyxia are ante-partum haemorrhage, placental infarction, and abnormality in the course of labour or delivery, the last being sometimes associated also with intracranial haemorrhage. The majority of cases in both groups had a history of one or more of these conditions, ante-partum haemorrhage and placental infarction being more frequent antecedents in the toxaemic group, and abnormal labour or delivery in the control group.

A substantial minority in the control group and a few in the toxaemic were due to gross developmental abnormality of the foetus.

An appreciable number remain in which no ante- or intra-partum factor can be held accountable for the stillbirth, and these include a few cases in which evidence of asphyxia was found at necropsy, but here again the greater number in the control than in the toxaemic group precludes the drawing of any deductions about possible toxins.

The conclusion to be drawn is that while stillbirth is commoner in toxaemic than in non-toxaemic pregnancy, its pathological causes in the two groups are essentially the same, the principal one being asphyxia. It thus appears that the presence of toxaemia renders the foetus more liable to be asphyxiated, presumably as a result of the higher incidence of ante-partum haemorrhage and placental infarction in toxaemic than in normal pregnancy. (The incidence of these conditions cannot, of course, be obtained from the figures given, which refer only to pregnancies whose outcome was in stillbirth, but that it is higher in toxaemic pregnancy is generally accepted.)

The neonatal death rate also is higher in the mature infants of toxaemic mothers than in those of non-toxaemic ones, although the difference is less than in the case of the stillbirth rate.

Necropsies were performed on the majority of the infants, and the findings in the toxaemic and control groups were again similar. The commonest cause of death in the first four or five days was asphyxia, with or without post-asphyxial pneumonia; intracranial haemorrhage was a less common cause. These two conditions accounted for the majority of the early deaths, and in most cases there was a history of ante-partum haemorrhage, placental infarction, or abnormality of labour or delivery. In this series, unlike the stillbirths, ante-partum haemorrhage was a commoner antecedent in the control group and abnormal labour or delivery in the toxaemic group. There was a high proportion in each group of infants of extreme prematurity; twenty-five in the toxaemic group and thirty-three in the control being below 2¾ lb. (1,250 g.) at birth; these infants might well be expected to die whether asphyxiated or not.

Asphyxia without any recognizable ante- or intra-partum cause occurred in a number of cases, greater in the control than in the toxaemic group,

and in most instances in extremely premature infants.

Deaths occurring after the fifth day were nearly all due to infection, the majority to pneumonia and a number to gastro-enteritis.

The cause of death remained undetermined in a few cases in each group. In this series toxic or degenerative changes were found in the liver and/or kidneys in four infants in the toxaemic and twelve in the control group; all were associated either with asphyxia or with infection, and none could be described as ' eclamptic changes '.

The causes of neonatal death, like those of stillbirth, are thus the same in the infants of toxaemic and of non-toxaemic mothers. The findings in this investigation support the opinion of Esch (quoted by Tunis) on the importance of prematurity and of difficulties in labour or delivery, and those of Tunis (1928) and Strauch (1939) on the additional role of disturbance of the placental circulation by placental infarction or ante-partum haemorrhage. Tyson and Bowman (1931) ascribed the high mortality among the infants of toxaemic mothers solely to premature birth, but this would seem to be unjustified. The point is of importance, for if prematurity were the sole cause of death in these infants then the interest of the infant would demand that pregnancy be allowed to continue as long as possible, whereas if it is increasingly subject to the risk of intra-uterine asphyxia its interest would coincide with that of the mother, which often calls for the termination of pregnancy before term, a living infant, although handicapped by prematurity, being preferable to a mature one which is stillborn or dies shortly after birth.

Drillien (1947a), who emphasizes the role of toxaemia in the etiology of premature birth and hence in that of neonatal death, suggests also that it may play an important part in causing intra-uterine deaths.

It is noteworthy that whereas in the control group all save one of the seventy-seven premature births were the result of spontaneous onset of labour, in the toxaemic group thirty-two out of sixty-one premature infants were born as the result of an induction of labour.

When the stillbirth and neonatal death rates for premature infants are separated from the general figures the odd fact emerges that the premature infants of toxaemic mothers actually fared better than those of non-toxaemic ones. This is in agreement with Ludlow's findings (1933), and also with those of Drillien (1947a); the reason for it is obscure. The surviving infants find their mothers' toxaemia no handicap, as they make at least as good progress as the infants of healthy women.

The greater part of this investigation has been concerned with mature living infants. If a toxic substance, whether of a hypertensive or other nature, is formed in the maternal organism, or more particularly in the placenta, and circulates in the maternal blood stream to produce the signs and symptoms of the toxaemia of pregnancy, it might be expected to enter the foetal circulation and produce its effects there also; were such a substance formed by the foetus it is hardly conceivable that it could produce such extensive effects upon the mother and none upon the foetus itself.

Ways in which maternal toxaemia might be thought capable of affecting the infant are, in addition to the particular features of oedema, albuminuria, and hypertension, impairment of general progress with less than satisfactory gain in weight and possibly undue sleepiness and slowness, and greater liability to infections.

Progress, as judged by gain in weight, has been shown to be as good in the toxaemic as in the control group.

While there were more lethargic babies in the toxaemic group than in the control, this may possibly be accounted for by inductions of labour and sedatives given to the mother before delivery. The only other explanation for undue sleepiness which might be advanced would be cerebral oedema occurring as part of a generalized oedema. Manifest oedema is rare in full-term infants; occult oedema would show itself in a big loss of weight in the first few days of life, and it has been shown that the initial loss is not significantly greater, weight for weight, in the toxaemic than in the control group.

Albuminuria was found considerably less often, in the small number of specimens examined, in the toxaemic than in the control group; small as the numbers are, the findings certainly do not support Salmi's statement that albuminuria is commoner in the infants of albuminuric than in those of healthy mothers.

The estimations of the systolic blood pressure gave an average first day reading lower in the toxaemic group of seventy cases than in the control group of 120 cases, though this difference is not observed in the smaller groups on which daily readings were made. The observed variation of the pressure with birthweight and length (the average birthweight being lower in the toxaemic group than in the control) does not account for this difference on the first day. The average eighth day reading was almost identical in the two groups. The few infants of severely toxaemic mothers on whom readings were made gave averages lower than the remainder in the toxaemic group. The daily readings in each group show no consistent form of curve, though in the great majority of cases the reading was 20 to 30 mm. higher on the eighth day than on the first.

The infants in the toxaemic group showed no greater liability to infection or any other morbid condition than the controls, and nothing resembling neonatal eclampsia, either clinically or pathologically, was encountered in the series of survivors or in the stillbirth or neonatal death series.

Summary and Conclusions

1. The incidence of stillbirth and the occurrence of neonatal death have been found to be higher in

infants born at term to toxaemic women than in the full-term infants of non-toxaemic women delivered in the same hospital. The principal cause in both cases is the greater liability to asphyxia resulting from ante-partum haemorrhage and placental infarction. No post-mortem evidence has been found to support the view that toxic changes in the foetus occur as the direct result of maternal toxaemia.

2. Full-term infants (of toxaemic mothers) who survived showed no greater liability to infection, and no less satisfactory progress as judged by gain in weight during the neonatal period, than the infants of non-toxaemic controls.

3. A higher incidence of neonatal oedema was found in the full-term infants of toxaemic mothers than in controls.

4. In a small series of cases, albuminuria on the third day of life occurred less frequently in the infants of toxaemic mothers than in controls.

5. A comparison has been made of systolic blood-pressure readings in full-term infants of toxaemic and non-toxaemic women during the first eight days of life, and the findings discussed.

6. The incidence of premature labour was found to be significantly higher in toxaemic women than in non-toxaemic women delivered in the same hospital during the same period.

7. The stillbirth rate and neonatal mortality rate of premature infants born to toxaemic women were lower than those of premature infants born to non-toxaemic women in the same hospital.

8. The progress, judged by gain in weight, of premature infants born to toxaemic women compared favourably with that of groups of premature infants of similar birthweights born to non-toxaemic women.

9. Lactation of toxaemic women was less satisfactory than that of non-toxaemic controls.

10. Severe toxaemia was found to have a more adverse effect on lactation than mild toxaemia.

I wish to thank Prof. R. W. B. Ellis and Prof. R. J. Kellar for permission to quote from the records of the Simpson Memorial Maternity Pavilion, and Dr. A. R. Macgregor for permission to quote post-mortem reports; also Dr. B. A. Woolf for advice on the presentation of graphs and tables.

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THE NOSE IN RELATION TO THE CEREBROSPINAL FLUID AND LYMPH STREAM

BY

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Introduction

In health the nose is the first part of the respiratory tract to receive the impact of air from outside, and the structure of the nasal mucous membrane is well adapted to respond to some of the changes in the composition and properties of this air. The response consists in part of saturating the inspired air with water vapour, and adjusting its temperature to that of the body; it also is instrumental in holding up particulate matter, and preventing a good deal of it from reaching the remainder of the respiratory pathway and lungs. If the air is cold it is warmed before it reaches the lungs, and for this reason the nasal mucosa is endowed with a high degree of vascularity, being rich not only in capillaries, but also in an abundance of arteriovenous anastomoses, in virtue of which it is capable both of rapid engorgement and of equally rapid shrinkage. If the inspired air is dry it is moistened as it is drawn through the nose, but the mechanism of this moistening is somewhat obscure. Though the nasal mucosa is rich in mucous glands, the moistening of the air requires not a mucous but a watery secretion or possibly transudation. The secretion of the healthy mucous membrane does in fact contain very little mucus, and it requires an abnormal irritant to evoke the full mucous secretion of which the nasal epithelium is capable.

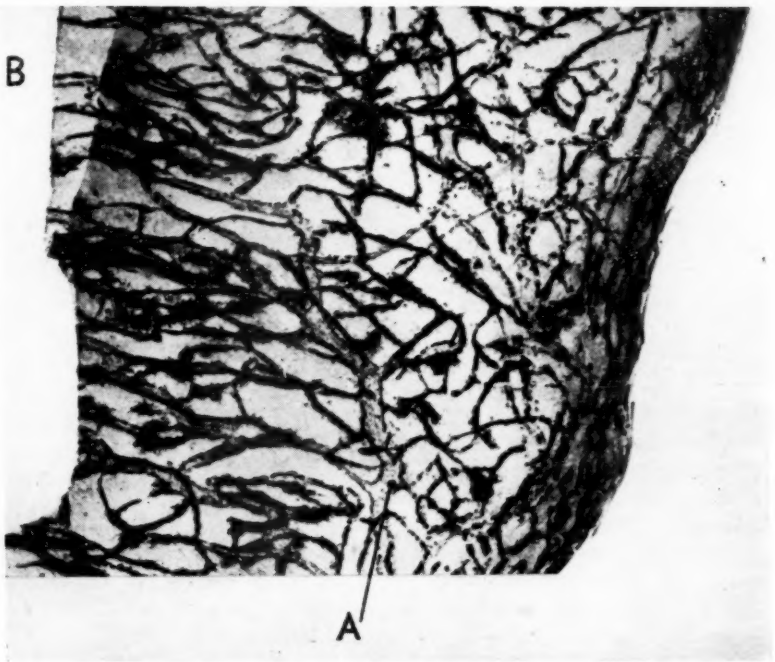
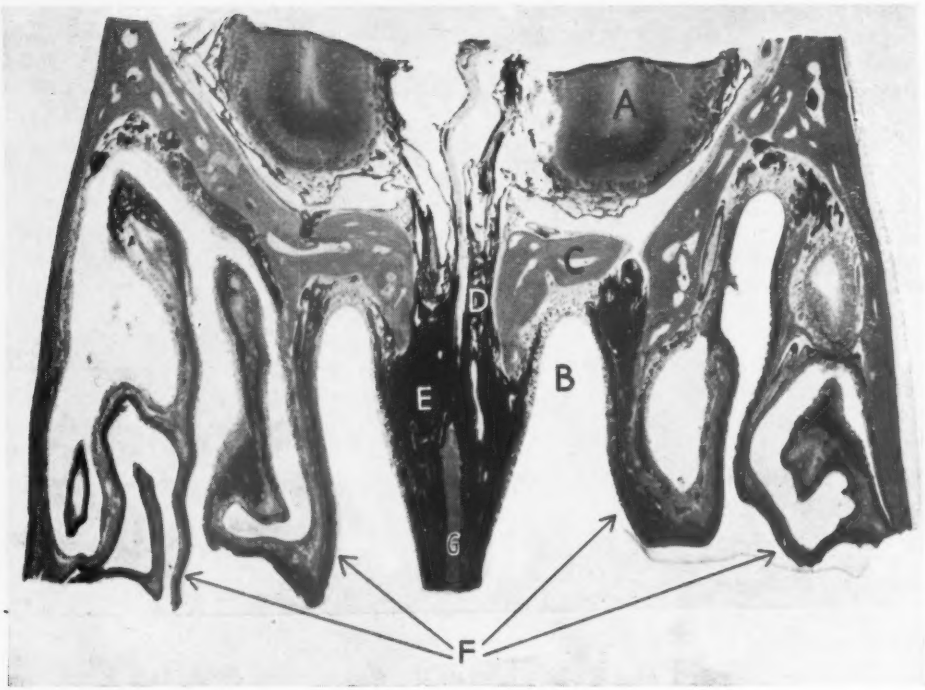


FIG. 1 (×50).—One of the turbinate bones from the same specimen as fig. 2. The smaller vessels are completely filled with ink, whereas in the larger vessels the lumen is almost empty, and the ink has adhered to the walls. The line marked A ends in one of these larger vessels. The turbinate bone has been cleared by the Spalteholtz technique, and then photographed by transmitted light. The plexus is present on both aspects of the bone, but in the top left hand corner, where the turbinate has been cut obliquely, the plexus on one side only is seen (B).

Particulate matter is to some extent held back by the nose, partly by the hairs in the proximity of the external nares, partly by the adhesive properties of the moist surface of the mucosa, the adherent particles being subsequently removed by increased secretion and ciliary action. If the particles are inanimate, for example, soot particles in a fog, this mechanism is fairly adequate. But if the particles are animate, such as viruses or bacteria, then if they are pathogenic they can invade the mucosa and multiply in it. Once they have invaded the mucosa, virus particles or bacteria can spread throughout its extent, and in this way may reach the accessory air sinuses, the lacrimal apparatus and eye, or the middle ear. But apart from this superficial mode of spread, infective particles may penetrate more



A = Olfactory bulb.
B = Roof of nasal cavity.
C = Cribriform plate.
D = Ink following the path of an olfactory nerve bundle.
E = Accumulation of ink round the terminal part of an olfactory nerve bundle, possibly an extravasation, since the injection was made under raised pressure.
F = Submucous lymphatic plexus in various turbinate bones.
G = Nasal septum.

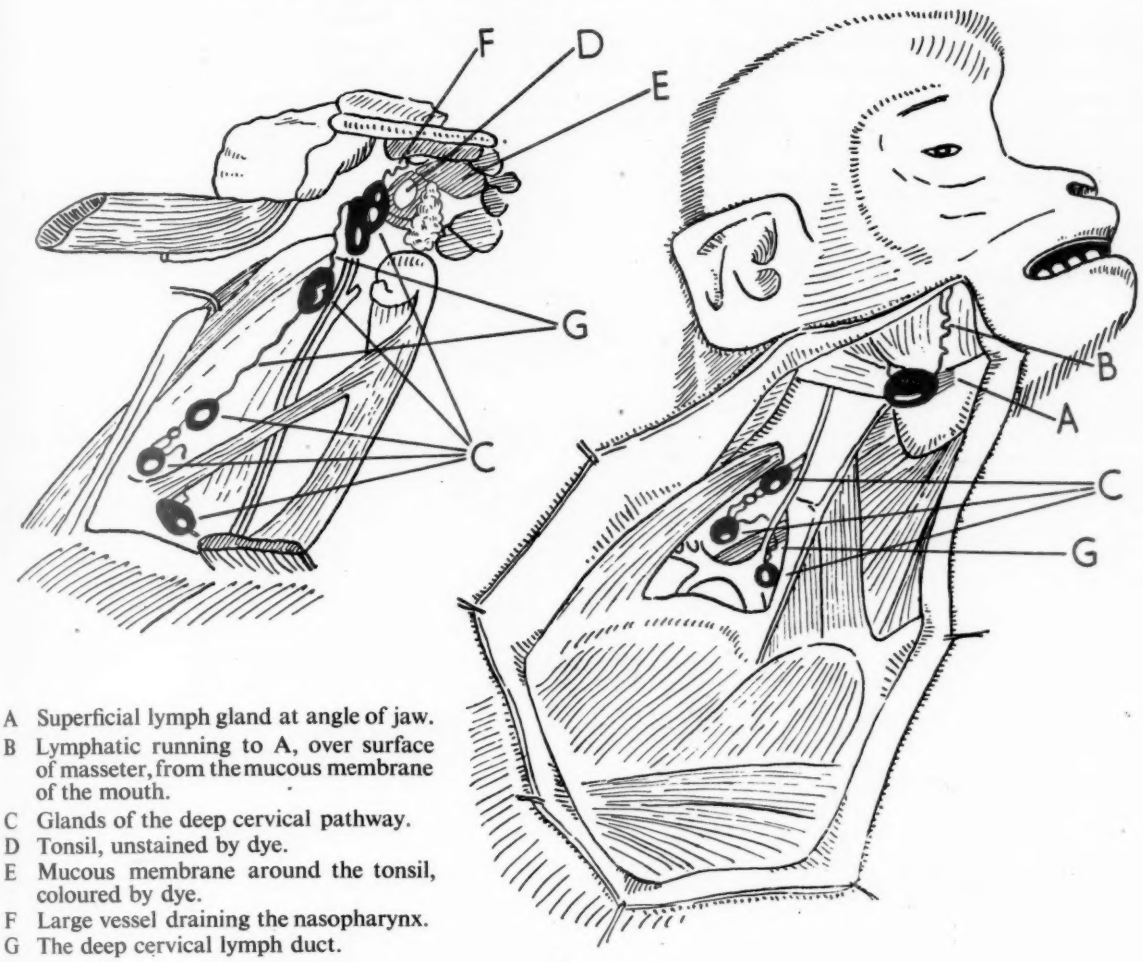
FIG. 2 (× 10).—Coronal section through the roof of the nose in a cat which had received under raised pressure an injection of indian ink into the cranial subarachnoid space. This shows the pathway taken by ink from the interior of the cranium to the submucous lymphatic plexus of the nose and the cervical pathway.

deeply and enter the submucous tissues. From the submucosa, viruses and bacteria can spread not only by direct extension, but also more rapidly and further afield through lymphatic and blood vessels, as well as along the paths provided by bundles of nerve fibres.

The submucous lymphatic plexus of the nose is unusually well developed. When a richly vascular area is subjected to rapid changes in its vascularity, and when, furthermore, its blood vessels are frequently exposed to such varying degrees of irritation, with consequent increase in the permeability of their endothelium, it is not surprising that there should on occasion be a rapid outpouring of fluid in its tissue spaces, giving rise to swelling and oedema which are not to be confused with vascular engorgement, though the two frequently co-exist. In the narrower respiratory passage of infancy, a relatively small amount of oedema will suffice to cause appreciable obstruction to the flow of air. Since it is important that the respiratory passages should be kept as clear and unobstructed as possible it is to be expected that a rich lymphatic plexus should be present in the submucosa, to facilitate rapid clearance of this oedema fluid. Fig. 1 illustrates the submucous plexus from one of the turbinate bones of a cat's nose, after injection with indian ink. From the point of view of illustrating the nature and density of the plexus, it is immaterial that this particular injection was made under pressure from the cranial subarachnoid space (fig. 2).

The Lymphatic Pathway

The rich submucous lymphatic plexus is drained by a well-defined lymphatic pathway, which can be demonstrated with great ease and in a most convincing manner by the instillation into the nose of a solution of vital dye (Yoffey and Drinker, 1938). Trypan blue is perfectly satisfactory, though Evans blue (T-1824), an isomer of trypan blue, is even better because of its more intense colour. The vital dye traverses the living mucous membrane and then enters the submucous lymphatics, whence it is drained by a number of collecting trunks descending from the posterior and lateral walls of the nasopharynx. These converge as they descend, and in most mammals drain into a single large lymph gland, close to the upper end of the internal jugular vein. From the lower end of this gland a single efferent vessel emerges, the deep cervical duct, or jugular trunk. This descends in close proximity to the internal jugular vein, and ends by opening on the right side into the right lymph duct, on the left side into the thoracic duct. The arrangement in the monkey (fig. 3) and man is essentially similar, except that the course of the lymph is interrupted by a chain of six or more small glands instead of a single large one.



A Superficial lymph gland at angle of jaw.
B Lymphatic running to A, over surface of masseter, from the mucous membrane of the mouth.
C Glands of the deep cervical pathway.
D Tonsil, unstained by dye.
E Mucous membrane around the tonsil, coloured by dye.
F Large vessel draining the nasopharynx.
G The deep cervical lymph duct.

FIG. 3.

The cervical lymphatic pathway in the monkey, demonstrated by nasal instillation of T-1824. Re-drawn from Yoffey and Drinker (1938).
The right hand figure is for orientation, and shows only the lower end of the deep pathway, which is shown in its entirety in the figure on the left

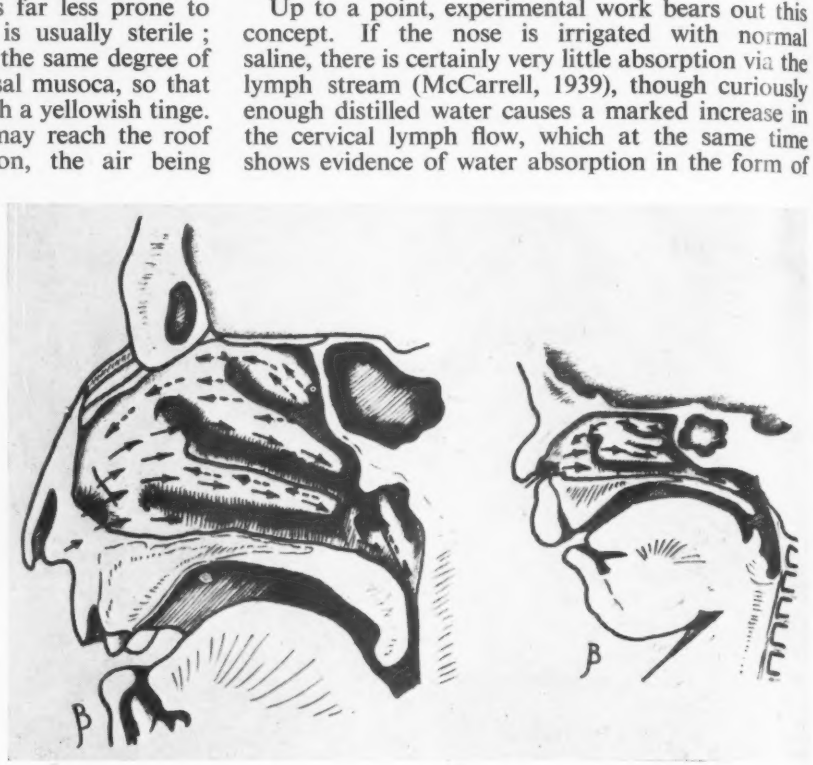
The entire complex may be termed the deep cervical pathway, and its main drainage area is the nose. The nasal instillation of T-1824 outlines the pathway a vivid blue, and indicates a pathway actually functioning. It constitutes a much more effective demonstration than the classical technique of interstitial injection, where the dye spreads in all directions from the site of injection, and gives no indication of the course taken by the lymph during life.

The Course of Air through the Nose

In the nose of the adult, inspired air is believed to traverse mainly the inferior meatus, and to a lesser extent the middle meatus, as well as flowing over the surfaces of the middle and inferior conchae. In fig. 4 the inspiratory current is indicated by solid arrows. The upper reaches of the nasal cavity, lined by the specialized olfactory mucosa, are above the inspiratory current and are not subject to the direct impact of inspired air. This would seem to follow from simple physical considerations, which also suggest that on a deep and powerful inspiration the rush of air against the sphenoid might cause some eddies in the roof of the nasal cavity. This is supported by the fact that one way of ensuring that air reaches the olfactory mucosa is by a powerful and deep inspiration. The other way in which inspired air may be manipulated for purposes of olfaction is to draw a small amount into the nose, and then impel it to the upper olfactory areas either by a gentle expiratory effort of brief duration, or by raising the soft palate. The first method, olfaction by deep inspiration, is the one adopted when the inspired air is known to be harmless, for example, filling one's lungs with a deep breath of country air; while the second method, sampling only small

quantities of air, is the one adopted when dealing with air about whose qualities one is in doubt.

Because of its position outside the main inspiratory current, the olfactory mucosa is far less prone to primary infection, and in fact is usually sterile ; furthermore, it does not require the same degree of vascularity as the rest of the nasal musoca, so that it tends to be somewhat pale, with a yellowish tinge. In expiration, rather more air may reach the roof of the nose than in inspiration, the air being propelled upwards by the expiratory vis a tergo, and not drawn through the lower part of the nasal cavity by suction at the posterior nares. But it is air which is already moistened and warmed, and freed from its particulate matter. The direction of the expiratory air current is indicated in fig. 4 by broken arrows. In the newborn infant (fig. 5) the vertical depth of the nasal cavity is much less, and the posterior nares are narrower not only absolutely, but also relatively, so that presumably even inspired air has access to the superior meatus.



FIGS. 4 and 5.—The lateral wall of the nose (about half natural size) in an adult (fig. 4), and a newborn infant (fig. 5). The probable direction of the air current is indicated by arrows (solid arrows=inspiration, broken arrows=expiration). In fig. 5 only the inspiratory current is shown.

The inspiratory air current is confined in the adult to the lower two-thirds of the nose, while the expiratory current reaches the upper olfactory area, which may also be reached (1) by diffusion if the air in the nose is kept still; (2) following slight movements of the palate; (3) on powerful and deep inspiration.

In the infant, apart from the diminished vertical depth, the development of eddies through the inspired air impinging against the sphenoid is probably much more marked than in the adult.

Absorption through the Nasal Mucosa

The passage of infective matter through the nasal mucosa is a special and peculiar instance of a much wider problem, namely that of absorption through the mucosa. At the commencement of vertebrate evolution, in fishes, the nose was part of the alimentary tract, and nose and mouth formed a single cavity. Though at a later period the development of the palate came to prevent ingested matter from coming into contact with the nasal mucosa, the latter has still retained certain powers of absorption.

As with the remainder of the alimentary canal, the first barrier to be passed by substances undergoing absorption is the mucous membrane itself, for the most part ciliated and columnar. It is perhaps to be emphasized that in the opinion of most observers the mucous membrane is a continuous layer, and does not possess the ' stomata ' described by Baum and Trautmann (1925-26). Once substances are through the mucous membrane, they are in close proximity to both blood and lymph vessels. Here one would expect that simple crystalloids and water could be readily absorbed through the blood capillaries, while somewhat larger molecules could be absorbed by both blood and lymph capillaries; the larger the molecule, the greater the lymphatic absorption and the less the absorption into blood capillaries.

Up to a point, experimental work bears out this concept. If the nose is irrigated with normal saline, there is certainly very little absorption via the lymph stream (McCarrell, 1939), though curiously enough distilled water causes a marked increase in the cervical lymph flow, which at the same time shows evidence of water absorption in the form of diminished protein content. Presumably the protein and salts in the submucous connective tissue attract water by osmosis, and then most of the water is absorbed into the blood, while relatively small amounts enter the lymphatics. This last point is one which is worth emphasizing, since the lymphatic system generally is only capable of handling small amounts of fluid.

Reference has already been made to the absorption of vital dyes after nasal instillation. It may further be noted that the dye passes through the mucosa within a few minutes and then appears in the cervical lymph, through the medium of which it finally reaches the blood stream, though some can also be absorbed directly into the blood capillaries. The total amount of dye absorbed is not very great,

even though the cervical pathway may be quite deeply stained.

Whether proteins are absorbed after nasal instillation depends upon their molecular weight. Thus egg albumen (molecular weight 34,000) can be readily detected in cervical lymph, serum albumin (c. 70,000) usually appears in traces, whereas serum globulin, as also horse serum, is never found in cervical lymph after nasal instillation, and presumably this is because it does not traverse the mucosal barrier (Yoffey et al., 1938). For if once it got through the mucosa it would be bound to enter the lymphatics, as is the case with any subcutaneous injection of serum.

The special property of the nasal mucosa in permitting the ready passage of T-1824 but not of horse serum has been used to demonstrate that when the dye is dissolved in horse serum the two become firmly associated. A 1 per cent. solution of T-1824 in normal saline, after nasal instillation, readily passes through the mucosa and can be identified in cervical lymph, but, if the dye is dissolved in horse serum, none appears in the lymph. However, if a 5 per cent. solution of dye in horse serum is employed, some dye does appear in the cervical lymph: presumably there is in the stronger solution an excess of dye which is not combined with the protein, and it is this uncombined dye which is free to pass through the mucosa.

Viruses and Bacteria

Ascending the scale of particle sizes, we find an essential difference between inanimate and living particles. Thus indian ink particles never penetrate the healthy mucosa, whereas viruses and bacteria may do so. This is more likely if one introduces pathogenic bacteria or viruses into a suitable animal.

It has been shown, for example (Schultz et al., 1938) that in the rabbit, which is very susceptible to pneumococcal infection, type III pneumococci readily traverse the nasal mucosa and appear in the cervical lymph. It is clear, of course, that the path taken by a highly virulent organism is determined not merely by particle size, but by complicating factors such as damage to the living mucosal and other cells. In these experiments the pneumococci were found in the lymph after it had already traversed the main cervical lymph node and was about to enter the blood stream. The experiments thus bring out the fact that in the case of virulent organisms lymph nodes do not constitute an effective barrier to the passage of bacteria.

With regard to viruses, Yoffey and Sullivan (1939) investigated the fate of vaccinia virus after nasal instillation in rabbit and monkey. From the point of view of size, virus particles are too large to pass through the mucosa. However, the virus can first establish itself in the mucosa and propagate, until presumably some invades the submucosa and then enters the lymphatics. Twelve hours after nasal instillation virus could readily be detected in cervical lymph, in which it was found at any subsequent period up to seven days after the primary infection of the mucosa. In all probability it would still have been detectable had the experiments continued over a longer period. Since the nasopharynx is so readily invaded by many viruses, the implications of these experiments are of considerable interest. It is clear that, from a nasal infection, a steady stream of virus can enter the blood and be disseminated throughout the body. In fact, it is difficult to see how, unless a virus has a specific tropism, this state of affairs could be avoided. Presumably a cold in the nose always becomes a generalized virus infection and is not limited to the nose itself.

The free and continuous passage of virus through the cervical lymph nodes is fundamentally different from the passage of bacteria, and depends upon the fact that the cytotropic virus particles become fixed to the cells of the lymph node. Most of these cells are lymphocytes which are proliferating and leaving the node to reach the blood stream. The lymphocytes thus act as virus carriers and very effectively disseminate virus throughout the body. As far as virus particles are concerned, therefore, lymph nodes not only do not afford a barrier to their spread, but on the contrary serve as a centre for the spread of infection. Furthermore, since a small number of lymphocytes is continually escaping from the blood capillaries to enter the connective tissue and the lymphatic capillaries all over the body (Yoffey and Drinker, 1939b), every lymph node in the body is in a position to become infected and serve as a further centre for virus spread. The same sequence of events presumably occurs in Jennerian vaccination, where enlargement and tenderness of the regional lymph nodes are usually easy to observe. The fact that the virus particles are carried by the lymphocytes, and are not free in the lymph, can readily be shown by centrifuging the lymph at low speeds. The virus-containing lymphocytes are thrown down, whereas the supernatant fluid does not contain virus. The lymphocytes can be repeatedly washed in saline without losing their virus.

It must be emphasized, however, that the lymphatic dissemination of viruses cannot apply to viruses with highly specific cytotropisms, for example, the neurotropic.

The Nose and the Interior of the Cranium

The roof of the nose is separated from the interior of the cranium by a thin sheet of tissue, namely the cribriform plate of the ethmoid bone, with dura-arachnoid on its cranial aspect, and nasal mucosa with submucous tissue on its nasal side. The entire tissue mass is of the order of thickness of 0·5-1·0 mm. in the adult and even less in the infant, and would seem to offer very serious possibilities for the direct spread of infection, through tissue continuity, from the nose to the cranium. The work of Rake (1937) was perhaps unnecessarily alarmist in this respect, particularly

since, in the adult, inspired air does not have access to the superior meatus, which is usually sterile. In the newborn infant the air with its bacteria has readier access to the superior meatus. This fact, in conjunction with the thinner and softer tissue barrier, since the cribriform plate is not ossified for some little time after birth, accounts no doubt for the greater ease with which in the infant infection may spread from the nose to the interior of the cranium. Even in the adult certain types of infection are believed frequently to reach the brain by this route. Among bacteria, one may instance the meningococcus.

As far as viruses are concerned, the specifically neurotropic viruses were once thought to have in the roof of the nose a particularly ready entry to the nervous system. The free processes of the olfactory nerve cells, projecting naked and unprotected into the cavity of the nose, seemed to afford an easy contact between neurotropic viruses and nervous tissue, with rapid spread along the fibres of the olfactory nerve, through the foramina in the cribriform plate, and so via the olfactory bulbs and tracts to the brain and spinal cord. It is indeed not so very long since attempts were made to destroy the olfactory nerve endings by dropping tannic acid into the nose, and producing thereby varying degrees of permanent anosmia, in an effort to prevent the dreaded virus of poliomyelitis from reaching the nervous system. However, we now know that this heroic sacrifice of one of the special senses was in vain, since the portal of entry of the virus is elsewhere, however plausible the hypothesis of olfactory spread may once have sounded.

But if viruses or bacteria do not spread by direct propagation along the individual nerve fibres, there is theoretically another route open to them, namely the spaces around the olfactory nerve bundles, and between their constituent fibres.

The emerging bundles of the olfactory nerve are surrounded by a space containing cerebrospinal fluid and continuous with the cranial subarachnoid space. This perineural space is bounded by a thin but definite condensation of connective tissue, which accompanies the nerve as far as the submucosa, where it ceases. This is opposed to the classical idea, according to which the pia mater was closely attached to the nerve as it passed through the plate, while the dura-arachnoid also passed through the foramen to fuse just below it with the pia. In this latter way there would be a wedge-like prolongation of the subarachnoid space around the olfactory nerve (Yoffey and Drinker, 1939a) as opposed to the newer concept (Field et al., 1948).

If an animal is anaesthetized and placed on its back, a solution of trypan blue or T-1824 dropped into the nose forms a pool in direct contact with the mucous membrane immediately below the cribriform plate. The dye quickly passes through the mucosa and enters the cervical lymphatic pathway, but never reaches the interior of the cranium, even though the animal is left on its back for as long as six hours. Now, whereas these colloidal dyes do not find their way into the cranium, a crystalloid such as potassium ferrocyanide readily does so (Le Gros Clark, 1929). Yoffey and Drinker (1939a) explained these facts by assuming that the dura arachnoid sleeve had the properties of a semi-permeable membrane through which there was always a slight downward or centrifugal flow of cerebrospinal fluid into the submucous tissue of the nose. Colloids could not pass through this membrane, whereas crystalloids could, and, if their rate of diffusion was greater than that of the centrifugal flow of cerebrospinal fluid, could easily enter the cranium. On this basis it is clear that crystalloids in the cerebrospinal fluid could very readily find their way into the submucosa.

However, in view of the revised concept of Field et al. (1948), this explanation needs to be modified somewhat. The critical region is the distal part of the olfactory nerve bundle, close to the mucosa, where there is apparently free communication between the submucous tissue spaces and the perineural space, along which crystalloids or colloids (or for that matter even particles) could ascend quite freely. But they would have to make the passage against the current of cerebrospinal fluid, and apparently it is only the crystalloids which can do this, since their diffusion rate is greater than that of the fluid.

What of movement in the reverse direction, namely from the cranial subarachnoid space down to the nose? In this case the movement is with the current, not against it, and it is not surprising that not only crystalloids, but also colloidal dyes, can pass from the cranial subarachnoid space to the submucosa of the nose, and thence be carried away by the blood vessels and lymphatics. This occurs with great ease even if the pressure of the cerebrospinal fluid is kept within physiological limits, and, in fact, if dyes are used, it is the best of all methods for delineating the entire nasal lymphatic pathway.

In regard to particulate matter, it has in the past been generally accepted that within normal limits of cerebrospinal fluid pressure, particles will not pass from the cranial subarachnoid space to the nose. In the absence of information concerning particle size, these statements are difficult to assess. Recently, Field et al. (1948), found that, in the rabbit, indian ink particles (average size $0 \cdot 5\mu$) could readily pass out of the cranium along the perineural spaces of the olfactory nerve bundles, and also track with great ease between their fasciculi at pressures which were carefully kept within the normal range.

The implication is that in any condition where there are bacteria or viruses in the cranial cerebrospinal fluid these may make their way to the nasal mucosa and the cervical lymphatic pathway, unless inflammation obstructs the flow of fluid in the perineural spaces. Bacteria might or might not be held back by the lymph glands of the cervical chain; but viruses, unless possessed of some very specific

tropisms, would pass through and infect the general blood stream. It was the frequent findings of virus in the naso-pharyngeal mucosa which convinced so many of the earlier workers on poliomyelitis that the nose must be the portal of entry. In the light of our recent work, it is more likely that the virus finds its way to the nose secondarily via the cerebrospinal fluid.

Practical Applications

In considering absorption from the nasopharynx, the question arises whether this property of the mucosa can be put to any practical use, or has any consequences of clinical significance. The answer seems to be that while absorption definitely occurs it is not on a large scale, and therefore only substances which are potent in small amounts can have any effect. An excellent example is a substance such as mecholyl (van Dellen et al., 1937), evidence of whose absorption is provided by the rapid physiological response of the organism. The classical studies of Blumgart (1922) on pituitary extract were followed by immediate practical application of the fact of nasopharyngeal absorption. In animal experiments it is possible to isolate the nasopharynx and ensure that it is the sole site of absorption. In man, however, the use of a nasal spray, as in the work of Peters and Allison (1929) on the production of immunity to scarlet fever toxin, introduces the added complication of inhalation and swallowing, so that one cannot be certain that one is dealing exclusively with absorption through the nose.

In the case of proteins, those of larger molecular weight can be disregarded. To this class, unfortunately, belong bacterial antibodies, consisting of the globulins. Proteins of lower molecular weight, however, even though absorbed in only small amounts, may under certain conditions give rise to very definite effects. For example, if sensitization to a foreign protein has occurred, the absorption of even slight amounts may cause severe anaphylactic symptoms, either local, or general. Hay fever would appear to be a case in point.

The absorption of toxins is not perhaps strictly comparable with that of indifferent substances, since toxins may have an injurious effect on the mucosa and the endothelium of the capillaries, whereby the process of absorption will be facilitated. With this proviso, there is ample evidence to show that diphtheria toxin can be absorbed in amounts sufficient to evoke a fair degree of immunity. In this connexion one may cite the earlier work of Dserzgowsky (1910) in the horse, and of Blumenau (1911) in man. More recently, Fraser et al. (1940) have elicited an antitoxin response to concentrated diphtheria toxoid applied to the nasal mucous membrane on small pledgets of absorbent cotton wool. The pledget was placed between the anterior end of the inferior turbinate and the septum, so that apparently absorption must have been purely nasal.

As far as bactericidal substances are concerned, there is little direct evidence of their absorption. But it is clear that if a molecule as large as that of egg albumen can be absorbed without great difficulty, and because of its size pass into the cervical lymphatic pathway rather than undergo direct absorption into the blood, then some of the newer antibiotics may possibly find a use in dealing with infections of the cervical lymph glands. The determining factor (apart, that is, from the properties of the antibiotic itself) is molecule size. If the molecule is too small, absorption will occur through the blood vessels of the submucosa, and hardly any via the lymphatics. What is needed is a molecule whose size will not be too great for it to pass through the nasal mucosa, but will be too big for it to be absorbed through the submucous blood vessels, so that absorption can only occur through the cervical lymphatic pathway. The peculiar arrangement of the cervical lymph glands in man, in the form of a chain through each member of which the lymph of the pathway must pass on its way to the blood, seems to lend itself admirably to disinfection of the entire chain if only the appropriate substance could be introduced into the lymph flowing from the nose.

The Cerebrospinal Fluid and the Nasal Mucosa

The passage of ink particles from the cranial subarachnoid space, in the perineural spaces of the olfactory nerves, suggests an appreciable centripetal flow of cerebrospinal fluid. We do not as yet possess any quantitative data on this point. Weed is generally credited with stating that 95 per cent. of the cerebrospinal fluid was absorbed through the arachnoid granulations and the venous sinuses, and only 5 per cent. would then be left for all other channels of outflow, including the perineural spaces of the olfactory nerves. I have been quite unable to trace the source of the statement, or the evidence on which it is based. But whatever the quantity of fluid escaping this way, it is finally delivered close to the nasal mucosa, in the olfactory area, and it may well be that some of it passes through the mucosa to reach its surface, and is mainly responsible for keeping this region of the mucosa continually moist. There is nothing intrinsically unreasonable in this, for if molecules such as egg albumen and serum albumen can pass through the mucosa, then water and crystalloids should certainly be able to do so. The concept, if substantiated, would bring us very close to the old Greek idea of the pituita. But however attractive it may be, whether scientifically or historically, it is still hypothetical, and lacks clear experimental proof.

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RENAL VENOUS THROMBOSIS IN THE NEWBORN

BY

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Thrombosis of the renal vein was first described by Rayer in 1837. This was followed in 1877 by Hutinel's account of forty-two cases of renal thrombosis, in thirty of which the condition was bilateral. Abeshouse (1945), in reviewing 228 cases of renal thrombosis of all varieties, found ninety-eight of these in children less than a year old, and of this total ninety occurred in infants during the first two months of life. Barenburg et al. (1941) reported five cases in a series of twenty-five necropsies carried out on infants with gastro-enteritis—a figure which suggests a rather high incidence in this selected group of cases. At the Birmingham Children's Hospital over a period of five years and out of a total of 1,430 routine post-mortem examinations, six instances of renal haemorrhagic infarction were found. In four of these cases the main renal trunk was thrombosed. In the remaining two cases the thrombosis was confined to the interlobular veins and was therefore detected only on microscopic examination (figs. 1 and 3). A survey of the literature was made by Morison in 1945, with particular reference to renal thrombosis and infarction in the newborn, and he includes a description of a series of fatal cases.

Renal thrombosis may be primary, that is, the thrombotic process originates within the renal venous system; or secondary, resulting from extension of a thrombus along the vena cava or tributaries of the renal vein. This latter variety is rare in childhood. Sandblom (1948) has further subdivided the cases arising during the neonatal period.

1. A primary, rare form with no obvious etiology, and predominating urinary symptoms.

2. The usual variety encountered in infancy, which is secondary to infection with dehydration, and in which the urinary changes are minimal.

Ante-mortem diagnosis of the condition is rare, due probably to the rapid dissolution which almost invariably follows the onset of symptoms. A case of unilateral thrombosis, of his first type, was described by Sandblom (1948), in which nephrectomy appeared to be a life-saving measure in a five-day-old infant. Campbell and Matthews (1942) had previously described two similar cases with recovery following nephrectomy. One of these was unique in that a correct pre-operative diagnosis was made.

So far as can be ascertained, there is no authentic account in the literature of survival following bilateral renal venous thrombosis. Such a case is here recorded, with the notes of two fatal cases.

Case Records

Case 1. W.K., a full-term male infant, weight 7 lb. 4 oz., was delivered with forceps on March 24, 1948. He made good progress until the twelfth day, when he became drowsy, fed reluctantly, and developed diarrhoea. His condition deteriorated rapidly during the next four days, the diarrhoea increased, and all feeds were refused during the twenty-four hours before his admission to hospital on April 9, 1948. He was by now extremely collapsed, the temperature being 100° F., the pulse 160, and respiration 40 per minute. His weight had fallen to 5 lb. 7 oz.; the features were sunken; the colour was ashen, and the extremities were cyanosed; the fontanelle was depressed; respirations were shallow and distressed. Pus discharged from a forceps wound over the right parietal region. No enlargement of the abdomen was detected. The child was put into an oxygen tent and intravenous administration of plasma and saline was begun. Penicillin was given intramuscularly at three-hourly intervals. Oral fluids were withheld during the first two days.

Progress. No urine was passed until eighteen hours after admission, when a few cubic centimetres of almost pure blood was collected. The respirations became laboured; both kidneys were now considerably enlarged, the left kidney more than the right. During the following forty-eight hours the condition deteriorated. The stools became watery and offensive, numbering between eight and ten a day. Gross haematuria persisted. The size of the kidneys by this time had increased even more and the abdomen had become distended. On the fourth day after admission the respiratory rate rose to 65 a minute and there was marked dyspnoea, presumably related to the uraemia, since the blood urea had reached the high level of 329 mg. per 100 ml.

By the seventh day the scalp infection had resolved and the urine was macroscopically clear. The blood urea level had fallen to 292 mg. per

100 ml. Weak breast milk feeds, an ounce at a time, were now tolerated. The diarrhoea improved gradually but the condition of the child remained critical until towards the end of the second week. Then definite improvement set in. He gained weight; the stools became normal, and the size of the kidneys decreased. The blood urea fell to 62 mg. per 100 ml. By the end of the third week the left kidney was still somewhat enlarged but the right was no longer palpable. The urine was now microscopically clear. He was discharged from hospital six weeks after admission in good general condition. The left kidney was still palpable. The urine was clear and the blood urea was 52 mg. per 100 ml. Weight on discharge was 7 lb. 4 oz.

His condition was reviewed at the age of four months. Intravenous pyelography showed a normal pelvic shadow with normal excretion on both sides. The blood urea level was then 41 mg. per 100 ml., and clinical examination was negative.

DIAGNOSIS. Although post-mortem examination or laparotomy are the only means of establishing an absolute diagnosis, a clinical diagnosis of bilateral renal thrombosis may reasonably be accepted in this case on the following grounds:

1. The occurrence of frank haematuria in the absence of urinary infection. The urine remained sterile and free from pus throughout the acute phase of the illness. The haematuria persisted until the end of the third week in spite of adequate dosage with vitamin K at the onset. A diagnosis of haemorrhagic disease of the newborn could therefore be excluded. It has been shown that infants with renal haemorrhage resulting from birth injury invariably succumb within the first twenty-four hours of life (Cruikshank, 1930).

2. Gross enlargement of the kidneys with their subsequent return to normal size. This, along with intravenous pyelography at a later date, eliminated the possibility of a congenital condition.

3. The high degree of renal insufficiency indicated by the uraemia.

Two outstanding features of the case described are: first, the remarkably high blood urea level attained; secondly, the return of the kidneys to apparently normal function within a few weeks, following such gross enlargement with almost complete suppression of function. So complete was the recovery that it seems probable that both recanalization of the thrombi within the renal vein or its tributaries, together with the development of a collateral circulation from the extrarenal veins, were the factors responsible.

This case is unusual in that it had the presenting signs and symptoms of both groups described by Sandblom.

Case 2. A male infant was admitted to hospital on the twelfth day with a history of failure to gain weight since birth and gastro-enteritis of twenty-four hours' duration. He was semi-comatose. The urine contained a moderate amount of albumin. The prothrombin time was 30 seconds (control 18 seconds). Death occurred three days later.

Autopsy revealed an enlarged right kidney which was grossly congested. The right renal vein was distended and contained a recent thrombus which filled the whole renal vein and extended into the inferior vena cava. The lungs showed patchy consolidation. Both middle ears contained pus.

Case 3. A female infant aged four weeks became fretful and sleepless on the day before admission. The stools were watery. The child succumbed the following day. Post-mortem examination showed a haemorrhagic infarction of the whole right kidney and of the lower pole of the left kidney. Recent thrombi were present in both main renal veins and in the longitudinal sinus.

Case 4. A prematurely born female infant was admitted to hospital on the first day of life. The birth weight was 2 lb. 7 oz. The general condition was feeble, and there was respiratory distress. Death occurred eighteen hours after delivery. At autopsy the lungs were found to be almost completely airless. There were numerous asphyxial subepicardial haemorrhages. The heart and great vessels were normal. The liver was grossly congested. Both kidneys showed areas of early haemorrhagic infarctions, 2 to 5 mm. in diameter. There were multiple subarachnoid haemorrhages over the cerebellum. The cerebral venous sinuses were normal.

HISTOLOGY. The medulla showed gross congestion but no necrosis. In the cortex there were areas of haemorrhagic infarction. In some places the renal parenchyma was completely replaced by red cells and numerous white blood cells. In other areas there was only disintegration of the tubular epithelium, the first convoluted tubules being more affected than the convoluted and Henle loops. The glomeruli were better preserved than the tubules (fig. 2). In several places thrombosis of the small veins was seen. Some were completely obstructed. In others a layer of hyalinized platelet thrombus was seen lining the wall of the vein (fig. 3).

Etiology

Sepsis and dehydration were the probable precipitating factors in the first and second cases described. In the third case dehydration was the only cause of thrombosis. Focal infection has been shown to be a frequent accompaniment of renal thrombosis, and in Case 1 the scalp infection may well have given rise to bacteraemia or septicaemia. The occurrence of dehydration, in conjunction with the normal relatively low venous pressure in the newborn, predisposes to thrombosis and accounts in part for the high incidence of the condition during the neonatal period.

Case 4 is unusual in that both infection and dehydration were absent. The thrombosis in this instance was presumably caused by the asphyxiated

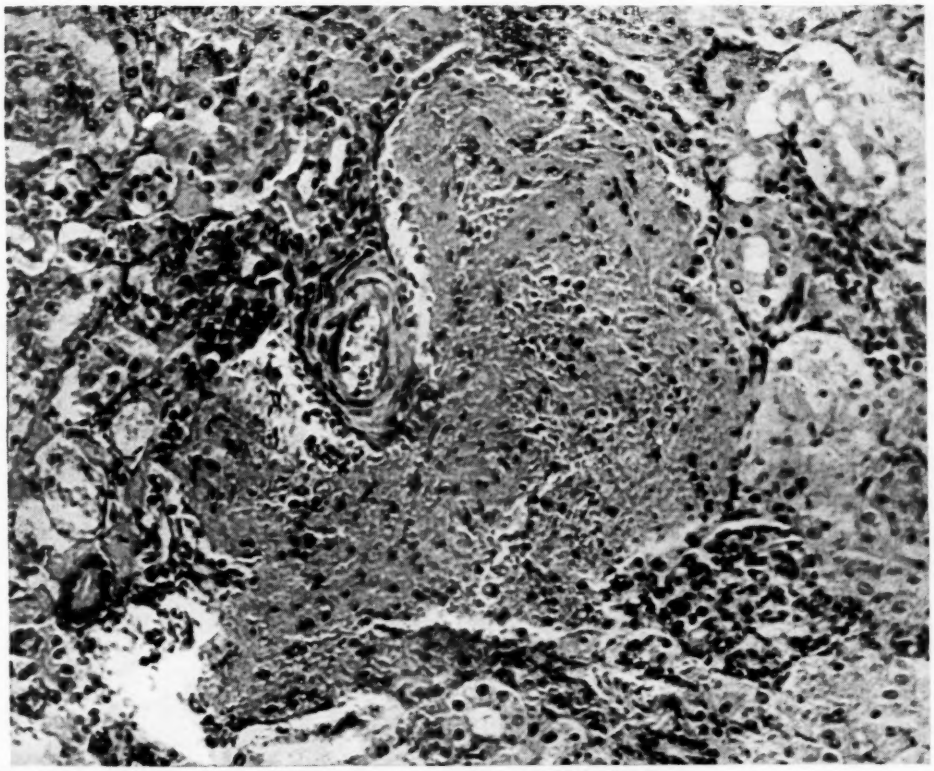

FIG. 1.—Thrombosis of renal vein in one of six cases discussed. ×120.

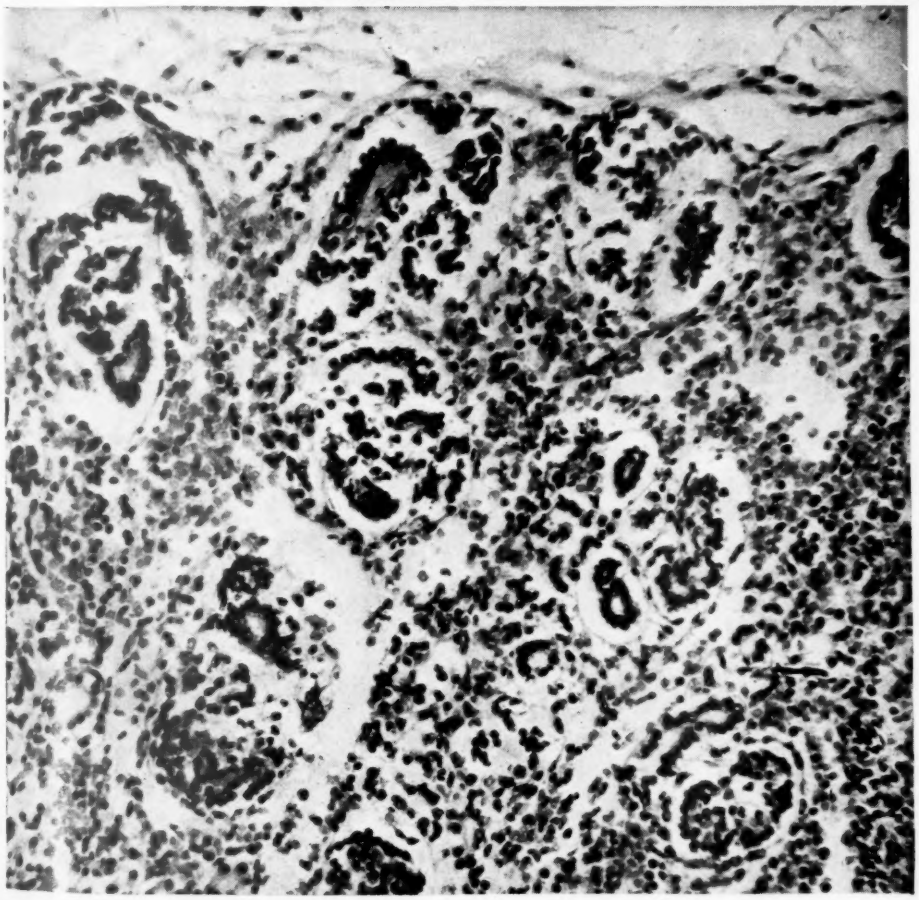

FIG. 2.—Haemorrhagic infarction of renal cortex in Case 4. ×120.

condition of the infant, which resulted in general venous congestion with stagnation. This etiology contrasts with cases hitherto described. Cruikshank (1930) in an analysis of eight hundred neonatal deaths, was unable to demonstrate any relationship between maturity, birth asphyxia, or marasmus and renal (as opposed to intracranial) thromboses.

Toxaemia per se has not been proved to play any significant part in the process.

Treatment

It is of interest that in Campbell's two cases treated surgically the prothrombin level, pre-operatively, was well below the average normal low level at that period of life. He advocates the administration of vitamin K in such cases. In Case 2, referred to earlier by the author, the prothrombin time was found, forty-eight hours before death, to be 30 seconds, a figure which may also be regarded as low, especially in view of the fact that 10 ml. of whole blood had been given intramuscularly on the day before admission to hospital.

As pointed out earlier, vitamin K did not influence the haematuria in Case 1 here reported. It is possible that the raising of the prothrombin level may, in fact, increase the risk of an extending thrombosis. It would seem reasonable, therefore, to avoid the use of vitamin K in any case of renal thrombosis which is to be treated medically, unless the child shows a general haemorrhagic tendency.

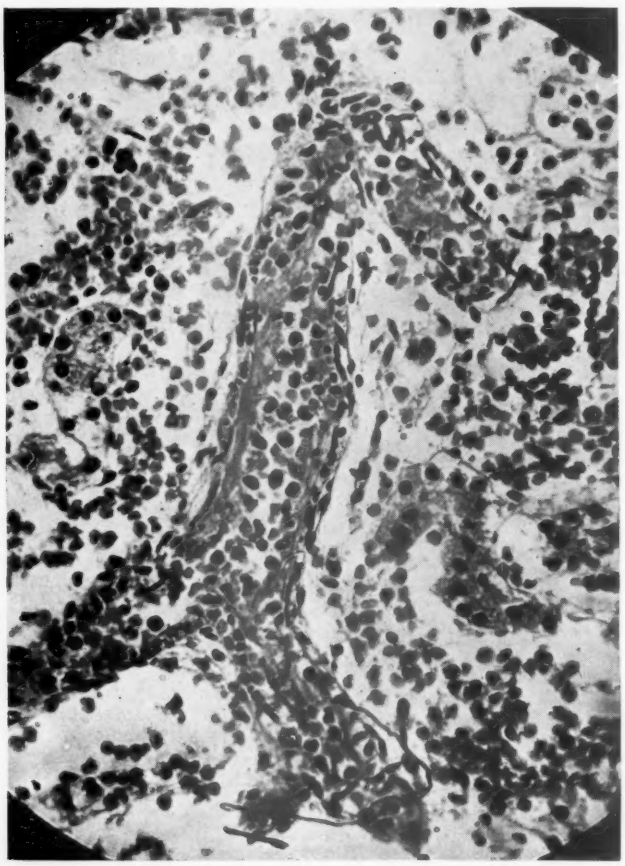

FIG. 3.—Early thrombosis of a small renal vein in Case 4. ×480.

Since the diagnosis of renal thrombosis is usually retrospective, there has been no opportunity for observing the effect of the anti-coagulant drugs.

The place of surgery in the treatment of renal thrombosis requires further consideration. Marshall and Whapham (1936) describe a case conforming to Sandblom's first group, in which the thrombosis is bilateral, and many similar cases are to be found in the literature. When a decision is made to remove a kidney in which thrombosis is suspected, a grave risk is being taken, since the possibility of a thrombotic process already having started in the other kidney is considerable. Unless there is a suppurative condition within the affected kidney it is difficult to foresee that nephrectomy, during the acute phase, will be of any benefit.

The criterion for surgery would appear to be, therefore, a heavily infected urine in a case of unilateral thrombosis.

The treatment of renal venous thrombosis may be summarized as follows:

1. Surgical treatment: nephrectomy is of value in certain selected cases of unilateral thrombosis.
2. Medical treatment: this should be directed towards (a) the relief of dehydration; (b) treatment of co-existing focal infection; (c) the prevention or treatment of urinary infection.

Summary

The literature concerning renal thrombosis is briefly reviewed.

A case of bilateral thrombosis with recovery is described in detail. Three fatal cases are described, including one of interlobular thrombosis due to neonatal asphyxia. The diagnosis, etiology, and treatment of the condition are discussed.

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CONGENITAL RIGHT-SIDED DIAPHRAGMATIC HERNIA

SOME DIFFICULTIES IN DIFFERENTIAL DIAGNOSIS AND OPERATIVE REPAIR

BY

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Right-sided congenital diaphragmatic hernia has in the past been considered to be incompatible with life. Even as recently as 1925 Hedblom stated that 75 per cent. of all cases of congenital diaphragmatic hernia die before the age of one month. With modern advances in technique death is now in most cases avoidable, and must be blamed on failure to diagnose correctly. Mis-diagnosis is so much the rule that in adult life diaphragmatic hernia has been called 'the masquerader of the upper abdomen,' and it has been calculated that on an average three incorrect diagnoses are made before the correct one is established (Harrington, 1945). In infants and young children, in whom cardio-respiratory symptoms often predominate, the diagnosis is even more likely to be missed.

In this paper two cases with right-sided congenital diaphragmatic hernia are described; in neither was the diagnosis established until several other tentative diagnoses had been discarded.

Frequency of Occurrence

Whilst it is certain that herniation on the right side is considerably less common than on the left, the comparative incidence of occurrence has not been accurately assessed. In the Frenchay thoracic unit approximately 3 per cent. of all admissions are cases of diaphragmatic hernia, and it is significant that the apparent incidence has risen appreciably since the adoption of the routine head-low prone position during radiological examination with barium.

On the right side herniation most commonly occurs through either the pleuro-peritoneal hiatus (Bochdalek) or the oesophageal hiatus; through the para-sternal hiatus (Morgagni) it is less common. It is important to recognize that apparently right-sided herniation may, in fact, arise from the oesophageal hiatus (figs. 1 and 2).

Symptomatology

The symptomatology is not appreciably affected by the site of herniation and varies between wide extremes. Cases may be discovered fortuitously (as in the two described below) or, in severe examples, death may occur within a few hours of birth.

It is said that symptoms are more severe in the congenital than in the acquired types of hernia, but in our experience the contrary is true: the congenital type frequently remains silent, whereas the acquired type often becomes dramatically obvious.

Cardio-respiratory symptoms. With congenital herniation cardio-respiratory symptoms tend to predominate. In severe cases dyspnoea and cyanosis may be evident soon after birth. They may persist or may recur paroxysmally, perhaps in relation to meals. Later in life palpitations or precordial pain may be described in milder cases.

Alimentary system. Disturbances of the alimentary system may occur with the above or alone. They arise in the main from variable degrees of obstruction either in the stomach or lower down in the intestines, and their manifestations are confusingly variable. If obstruction becomes complete, as not infrequently occurs, symptoms typical of acute obstruction develop and the outlook is gloomy indeed. In the absence of complete obstruction a common symptom is vomiting, though in mild cases there may be no more than eructation and a feeling of distension after meals. Occasionally haematemesis or melaena occurs from engorged mucosal vessels, and if bleeding is persistent the vague symptoms of anaemia may develop. In Case 2, described below, the gall-bladder was situated in the thoracic cavity, and in another recent case the intestines were imperfectly rotated and the appendix lay in the thorax; inflammation arising in any of the misplaced abdominal organs can obviously produce obscure symptoms whose interpretation may be perplexing.

General symptoms. Of the general symptoms, it has already been mentioned that some may be attributable to anaemia. In infants and young children there may be failure to thrive, probably due to a combination of cardio-respiratory and alimentary disturbances. In a recent case, at ten months of age an infant weighed little more than two pounds over its birth-weight; both the general condition and weight improved dramatically after operation.

Diagnosis

History. By the history alone the diagnosis can be only suspected. Excluding the most severe cases,

the common story (as in Case 2) is that of so-called recurrent pneumonia. This erroneous diagnosis is usually based on the evidence of dyspnoea and abnormal physical signs obtained when the child is examined because of some unrelated upper respiratory infection. Apparently inexplicable vomiting which recurs over a considerable period should also suggest the diagnosis.

Clinical examination. This may, on occasion, provide an unequivocal diagnosis. The essential feature is the detection of bowel sounds in the chest. To elicit this pathognomonic sign it is advisable to auscultate soon after the patient has taken a meal, and to continue auscultation for at least ten minutes. In both the cases described with these precautions the characteristic bowel sounds were invariably heard; without them they were frequently not detected. It has long been realized that even in the presence of a known diaphragmatic hernia abnormal signs in the chest may be absent; possibly the observance of the above precautions would reduce the number of such failures.

In addition, the variability of the physical signs from time to time in the same patient is itself suggestive of the diagnosis. Impairment of expansion on the affected side, dullness to percussion, and suppression of breath sounds, constitute the usual findings in the chest, and the mediastinum may be displaced. Occasionally the signs simulate those of pneumothorax or hydro-pneumothorax. The liver may lie in the thoracic cavity, and the physical signs which it produces are very commonly attributed to pleural effusion. If the duodenum is obstructed and the stomach consequently dilated, a characteristic splash may be elicited. When large portions of the bowel are contained in the chest the abdomen may fail to develop proportionately and may present a scaphoid appearance.

Radiological Appearances

In every suspected case radiological studies are essential, especially in view of the danger inherent in diagnostic aspiration where portions of the bowel are contained in the chest.

Only conditions occurring on the right side which are commonly confused will be considered here, though in theory similar appearances might be produced by 'gas' infections of the pleura, eventration of the right diaphragm with upward protrusion of part of the liver, multiple tuberculous cavities, congenital cystic disease of the lungs, hydatid cysts that have ruptured into the bronchial tree, and diverticula of the oesophagus.

The radiological appearances are suggestive because of their very oddity. There may be shadowing at the base which is 'typical of nothing.' The consistency of the shadow is not completely uniform, with a rare exception: if omentum alone has herniated the opacity may appear homogeneous. An appearance of 'tenting' is not unusual (fig. 3). If lateral views of the chest are studied in conjunction with antero-posterior views there should be little difficulty in distinguishing herniation from free pleural effusion.

The commonly accepted statement that radiological diagnosis can be made easily by three features, the detection of gas bubbles, collapsed lung, and mediastinal displacement, misleads by over-simplification.

In most cases diagnosis is indeed suggested by the presence of gas shadows and the characteristic pattern caused by the valvulae conniventes of the small intestines and the haustration of the large but this appearance may be simulated by (1) lung abscesses or saccular bronchiectasis (figs. 4 and 5); (2) loculated or encapsulated effusions; (3) loculated sub-diaphragmatic abscess; (4) interposition of colon between liver and diaphragm (fig. 6) or, (5) congenital abnormalities of the oesophagus. Collapse of lung and mediastinal displacement occur in varying degree, but are only subsidiary in diagnosis.

Certainty of diagnosis can be achieved by means of barium follow-through studies (figs. 7, 8, 12, 13). In no case should the precaution be omitted of tilting the patient in the prone position with the head low during the examination.

Lateral views with barium in the intestine help in localizing the position of the diaphragmatic defect, but to assess the size of the defect from radiological appearances is usually impossible.

Treatment

The treatment of the condition is always surgical. It should be undertaken as early as possible to avoid first, the technical difficulties caused by failure of expansion of the abdomen, which becomes progressively and relatively more marked the longer the abdominal contents remain in the thorax; second, the general maldevelopment which accompanies long standing disturbances of intestinal function; and third, the occurrence of acute intestinal obstruction. If obstruction does occur, surgical treatment becomes a matter of extreme urgency.

Two routes are available, the abdominal and the thoracic. The thoracic approach permits a sounder repair of large diaphragmatic defects, and an increase in the size of the abdominal cavity by raising the attachments of the diaphragm to a higher level in the thorax. Following replacement of the abdominal viscera the lung can be expanded without difficulty by the anaesthetist, and any structural change in the lung following the prolonged compression by displaced abdominal viscera is unusual.

In both the cases reported the defect was so large that the usual repair with an overlap was out of the question. Various methods of overcoming such a difficulty have been devised. Harrington's (1948) technique of performing a basal thoracoplasty to free the diaphragm has the disadvantage of being a deforming operation which interferes permanently with the function of the affected side of the chest. A new procedure was evolved, and proved successful in both cases. The chest was entered through the bed

of the ninth rib. After replacement of the abdominal viscera, the remnants of the diaphragm were freed from their attachments to the costal margin all round, and left with only their mediastinal origin and corresponding blood and nerve supply intact. The diaphragmatic defect was then closed by two rows of interrupted sutures of stainless steel wire and an overlap. The repaired diaphragm, much reduced in size, was reattached to the thoracic wall at a level two interspaces higher than normal with interrupted sutures of the same material, no difficulty being encountered in bridging the lesser distance horizontally across the thoracic cavity, after eliminating the costo-phrenic sulcus. The phrenic nerve was not crushed in either case, and the functional result has proved excellent in both patients.

Case Reports

Case 1. A girl aged 7 years was found on routine chest examination by a school medical officer to have abnormal physical signs in the right chest. She was sent to the local tuberculosis dispensary where a radiograph of the chest was taken. A diagnosis of right-sided pleural effusion was made, and the child was admitted as an emergency to a children's sanatorium with instructions to the resident medical officer to 'aspirate the chest.' The resident medical officer elicited from the mother a history of recurring bouts of abdominal pain and vomiting. The attacks had been irregular and bore little relationship to meals. There were no symptoms suggestive of pulmonary disease. Examination revealed an under-nourished and under-developed child; the lower half of the right chest was dull to percussion and breath sounds were replaced by bowel sounds, but this sign was elicited only on prolonged auscultation. The abdomen was scaphoid in appearance. A radiograph revealed a dense shadow in the lower half of the right chest with a few gas-containing areas showing typical intestinal haustration towards its peaked upper margin (fig. 3). A barium follow-through examination revealed the presence of half the duodenum, which was partially obstructed, the whole of the small intestine, and the right half of the colon within the right pleural cavity. Had thoracentesis been performed before an accurate diagnosis had been made, disaster would almost surely have followed.

The child was transferred to the Frenchay thoracic unit and, after a preliminary course of breathing exercises lasting four weeks, the hernia was repaired through the thoracic approach. No hernial sac was present. Replacement of the viscera was difficult owing to the contraction of the abdomen. The defect in the diaphragm, a patent pleuro-peritoneal canal, was so large that the plastic repair with transposition to a higher level, as already described, was necessary. The lung was inflated without difficulty and the chest closed without drainage. Convalescence was uneventful. The child has remained free from symptoms, and examination five years later showed normal development. X-ray examination shows that the right diaphragm moves normally, the right lung is fully expanded, and there is no impairment of thoracic function (fig. 9).

Case 2. A girl aged 4 years was admitted to hospital with a diagnosis of right basal 'pneumonia.' The mother reported two similar attacks of pneumonia, also on the right side, during the previous year. On admission the child was pale, looked ill, and had an intermittent cough; the temperature was 101° F., and the pulse rate 130, and respirations 40 per minute. Examination revealed poor movement, impaired percussion note, diminished breath sounds, and poor vocal fremitus at the right base. A diagnosis of pneumonic consolidation with a pleural effusion was made. Penicillin therapy was commenced. Eleven days after admission the dullness at the right base was less marked and bowel sounds in the chest were detected for the first time. Review of the radiographs suggested the presence of intestines, containing mostly fluid but also a little gas, within the right pleural cavity (figs. 10 and 11).

Further x-ray examination showed appearances more typical of a diaphragmatic hernia, and a barium follow-through revealed that the whole of the small bowel and the right half of the colon were in the right pleural cavity (figs. 12 and 13). The temperature, pulse rate, and respiration rate quickly dropped to normal, and penicillin was discontinued after twelve days. Breathing exercises were started.

Four weeks after admission a right thoracotomy was performed through the bed of the ninth rib. No hernial sac was present. Part of the duodenum, the whole of the small bowel, the right half of the colon, and the liver lay free in the pleural cavity. The right lung was collapsed. The gall bladder was in contact with the axillary part of the thoracic wall. Any attempt to needle the chest might have produced bizarre and dramatic consequences. Following replacement of the abdominal viscera the defect was again found to be too large for a simple repair, and a similar operation to that performed in the previous case was necessary. Convalescence was uneventful. The child has remained free from symptoms since the operation, her general condition is excellent, and on x-ray and screening the reconstructed right diaphragm appears to function normally (figs. 14 and 15).

Summary

1. The symptomatology, diagnosis, and differential diagnosis of right-sided congenital diaphragmatic hernia are reviewed.

2. A new technique for the plastic repair of large diaphragmatic defects is described.

3. Two cases successfully treated surgically are reported.

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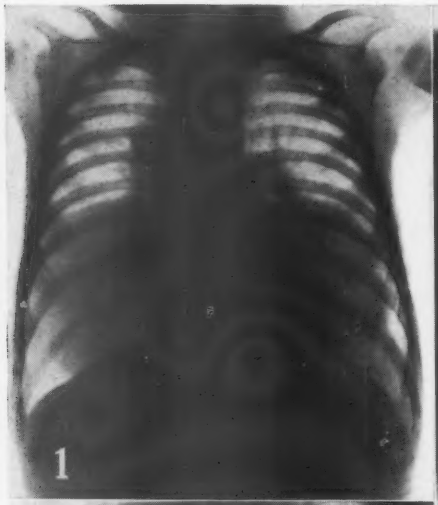
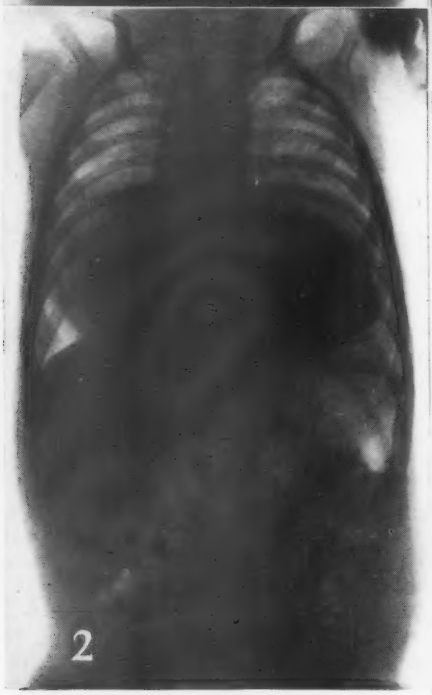
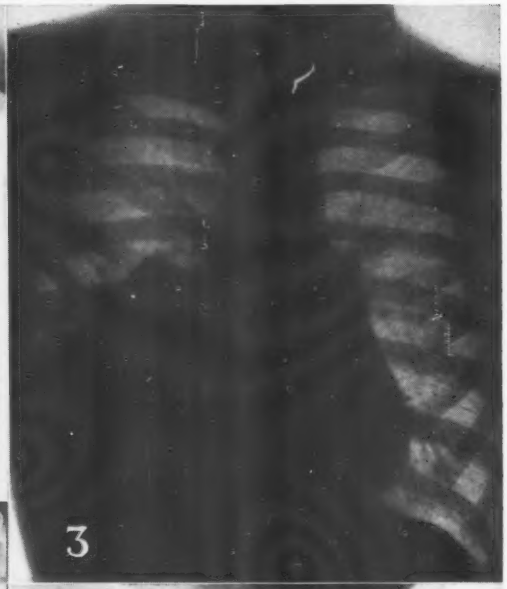
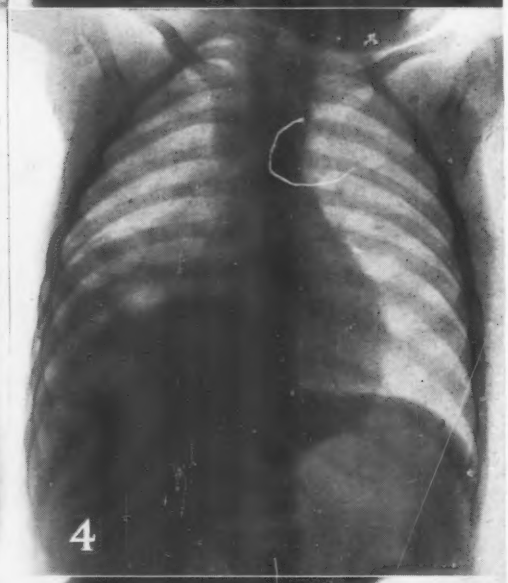








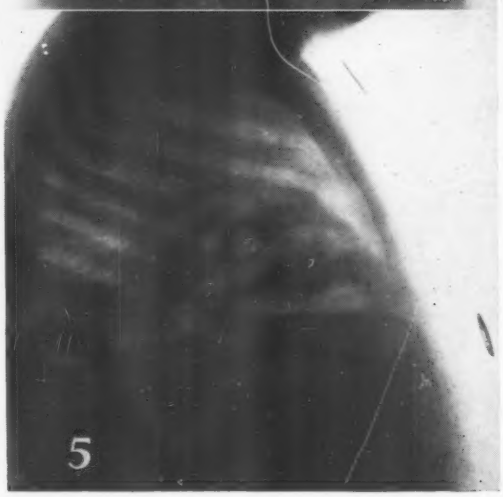


FIG. 1.—Hiatus hernia in infant (9 months old) projecting into both pleural cavities. Antero-posterior chest film.

FIG. 2.—The same, following barium meal.

FIG. 3.—Girl, aged seven years. Pre-operative film showing 'gas bubbles' and 'tenting' of the shadow at the right base. (Case 1.)

FIGS. 4 and 5.—Saccular bronchiectasis of the right middle and lower lobes in a child of eighteen months, simulating bowel shadows in the right pleural cavity.

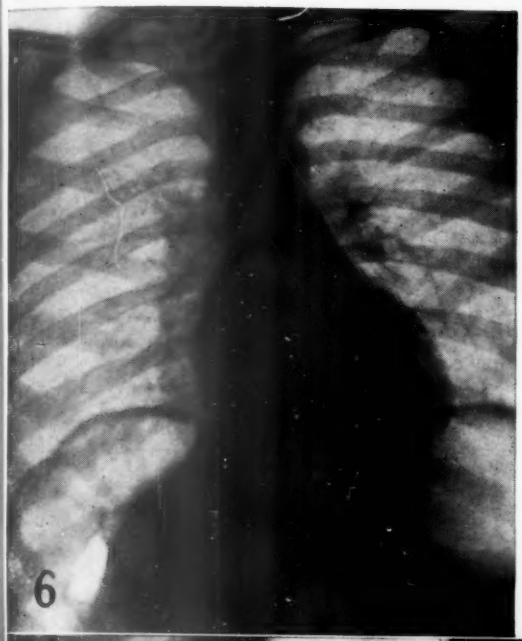
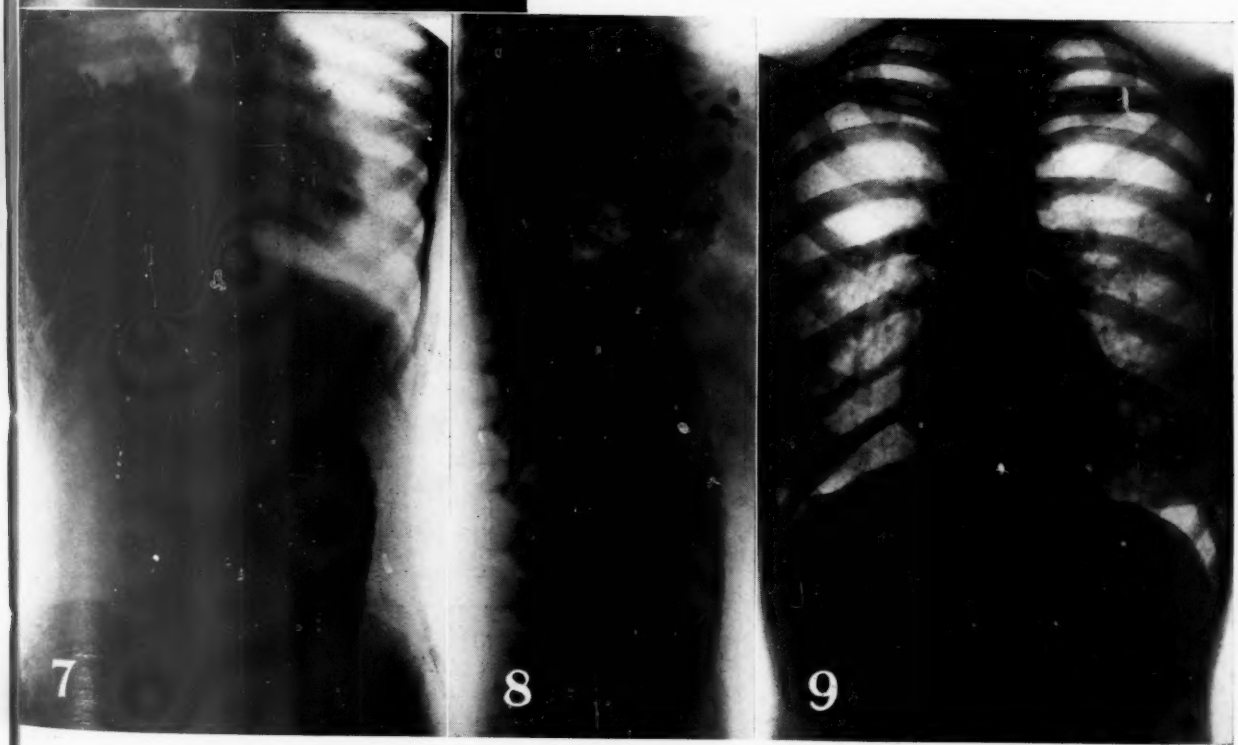
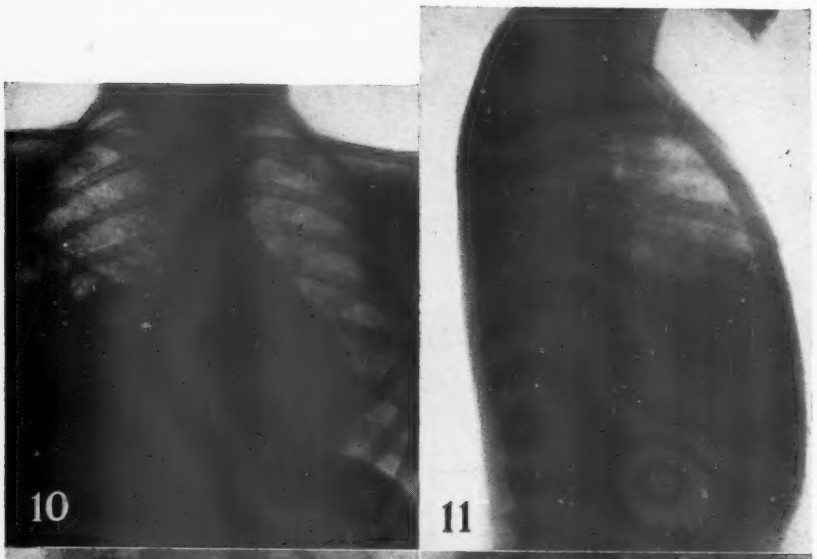


FIG. 6.—Interposition of colon between the liver and the right diaphragm.

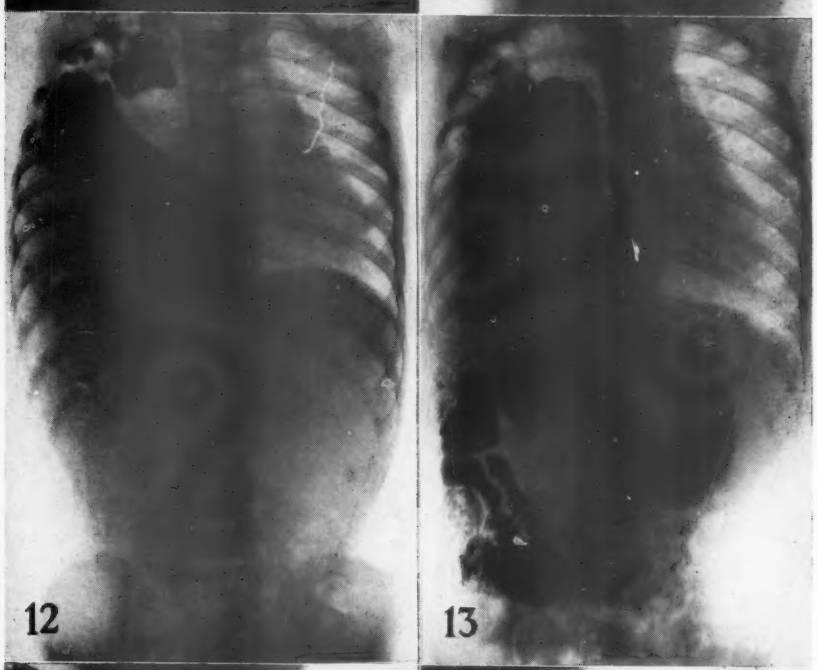
FIGS. 7 and 8.—Barium meal showing small intestine lying freely in the right pleural cavity.

FIG. 9.—Antero-posterior chest film five years after operation. (Case 1. Five years after operation.)

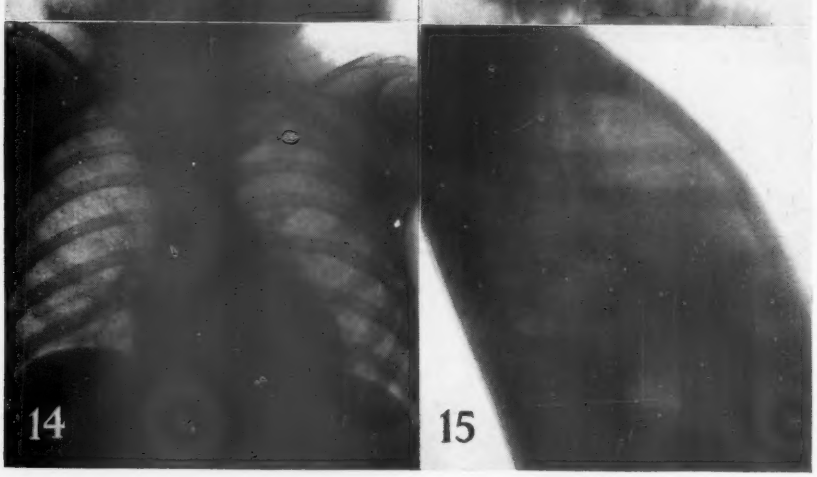




FIGS. 10 and 11.—(Case 2.) Antero-posterior and lateral films of chest showing 'gas bubbles' and 'tenting' of the opacity at the right base.



FIGS. 12 and 13.—(Case 2.) Barium meal in prone head-low position; both small and large intestine lying free in right pleural cavity.



FIGS. 14 and 15.—(Case 2.) Post-operative film of chest following repair; right diaphragm functioning normally.

CASE REPORTS

FUGITIVE PERICARDITIS

BY

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The following case is reported as an example of a little known complication of primary tuberculous infection.

A female child aged two and a half years was admitted to Southmead Hospital, Bristol, on Dec. 3, 1946. Her parents and sister were in good health and no history of tuberculosis was obtained. Apart from mumps at the age of two years, the child had been well until an attack of measles a month before admission. She was left with a cough and failed to regain her usual vigour. On Nov. 30, 1946, she refused her food, became pale, dyspnoeic, and distressed.

On examination on admission she looked pale and ill and was orthopnoeic. The temperature was 98° F., and the pulse 120 per minute, regular, but of poor volume. The cardiac impulse was diffuse and wavy and the apex beat was in the sixth left interspace in the anterior axillary line. A loud pericardial friction rub was audible all over the precordium; the heart sounds were muffled, but there were no murmurs. There were no signs of pulmonary or systemic congestion. At the apex of the right lung the percussion note was impaired, the breath sounds being tubular and the voice sounds increased. There were no adventitious sounds. An x-ray of the chest showed a greatly enlarged cardiac silhouette, a suggestion of fullness at the right hilum, and an opacity at the apex which was considered to be due to collapse or consolidation of part of the right upper lobe. An electrocardiogram

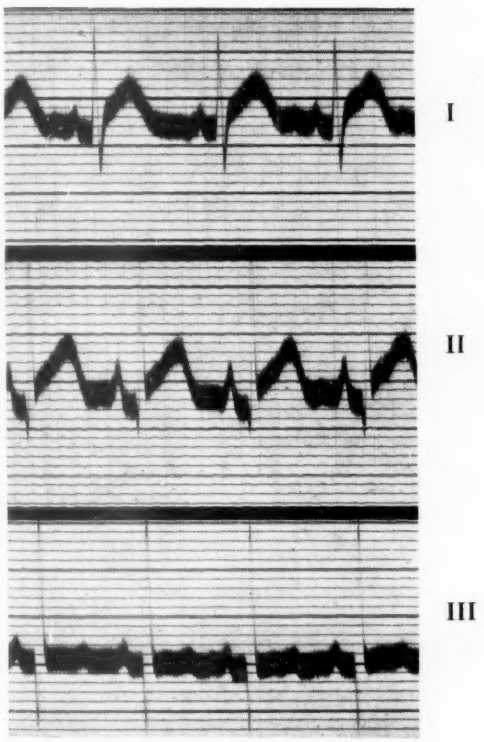

FIG. 1.—Electrocardiogram on Dec. 7, 1946, showing elevation of the S-T segment in leads I and II.

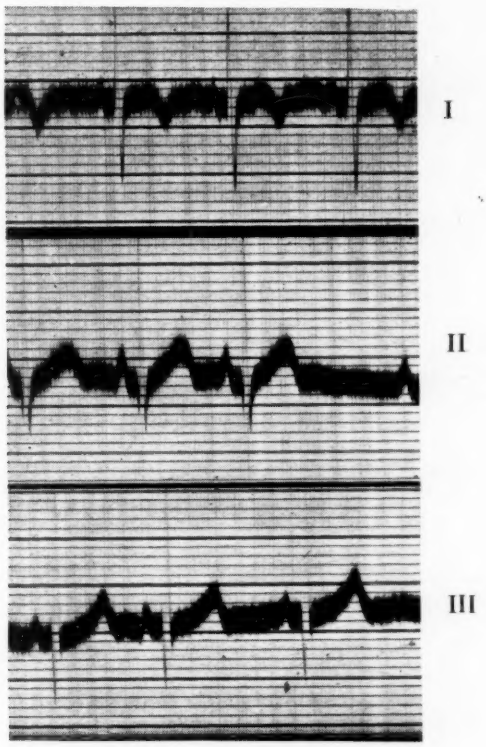

FIG. 2.—Electrocardiogram on Dec. 11, 1946, showing inversion of T wave in lead I.

showed in addition to tachycardia, elevation of the S-T segments in leads I and II (fig. 1). A blood count showed haemoglobin 102 per cent. and white cells, 7,000 per c.mm., with a normal differential.

Eighty thousand units of penicillin were given daily in divided three-hourly doses for a week. The child remained critically ill for three days, but subsequent improvement was rapid. By Dec. 11 an x-ray showed some clearing of the opacity at the right apex, and in the cardiogram the T wave was inverted in lead I (fig. 2). The Mantoux test was positive on that date.

Improvement continued until Dec. 18 when her transference to an isolation hospital was necessitated by an attack of chickenpox. An x-ray of the chest taken on Jan. 9, 1947, showed a normal sized heart and almost complete clearing of the right apical opacity. She was sent for convalescence on Jan. 15. When seen three months later the child's health was fully restored, her lung fields were clear, and her heart was normal. She was kept under observation for a further nineteen months and remained well.

Discussion

While the etiology of this case remains in doubt there are reasons for regarding it as an example of benign pericarditis associated with a primary tuberculous complex as reported by Wallgren (1947). This author described two patients with the combination of pericarditis and a primary tuberculous complex. His first case developed pericarditis one month after the onset of an illness characterized by fever and enlargement of the left hilar glands. A tuberculin skin test was positive soon after symptoms were noted. The child was ill for two months and then went on to make a complete recovery which was maintained for the subsequent three years of observation. His second case was very similar: again there was fever and enlargement of the hilar glands, and in addition erythema nodosum. Recovery was equally rapid and good health was maintained three years later. The excellent prognosis and freedom from relapse were especially stressed.

Wallgren stated that the acute benign pericarditis of his two cases was comparable to that of acute tuberculous allergic serofibrinous pleurisy and differed from the usual tuberculous pericarditis in that recovery was rapid and complete. In view of the favourable prognosis an analogy with the tuberculous serous meningitis described by Lincoln (1947) is also suggested. The interval of one month between the initial infection and the complicating pericarditis corresponds to the stage of generalization of the infection when miliary tuberculosis or tuberculous meningitis most often develops. As Wallgren pointed out this raises the possibility of a blood stream infection of the pericardium, but direct extension from enlarged mediastinal glands is just as likely.

The case reported bears a close resemblance to Wallgren's two cases. The symptomatology, positive Mantoux test, radiological appearances, recovery, and subsequent good health show a similar trend of events. This case was much younger than Wallgren's: two and a half years compared with nine years and six years.

An alternative diagnosis which must be considered is acute rheumatism, but the age of the patient, the absence of suggestive symptoms and signs during the acute stage, and of any relapse during the next twelve months, is against a rheumatic etiology. Pneumonia with purulent pericarditis was considered in the differential diagnosis, but was excluded by the course of the illness.

Summary

A description is given of pericarditis associated with a lung lesion and complete recovery within two months. It is suggested that this is an example of acute benign pericarditis associated with a primary complex as described by Wallgren (1947).

I wish to thank Dr. P. Phillips, medical superintendent, Southmead Hospital, Bristol, for permission to publish this case.

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CONGENITAL TOXOPLASMOSIS

REPORT OF TWO CASES

BY

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Infection of man with the protozoon toxoplasma in its various manifestation has now been described in an extensive literature mainly from America, but also more recently from Sweden (Magnusson, 1947), Denmark (Boesen, 1948), Holland (Binkhorst, 1947), and Switzerland (Bamatter, 1947).

With the exception of the case report by Jacoby and Sagorin (1948), published after this paper had been prepared for press, no other reports of cases of toxoplasmosis which can be regarded as established have been printed in this country. Reference should be made to the three cases described by Parsons (1946), though these were not confirmed by serological tests, and were later considered as not fulfilling the criteria provisionally required to justify the diagnosis of toxoplasmosis.

Though one of the earliest descriptions of the disease may be ascribed to Janku (1923), the condition was first summarized and proved by animal transmission by Wolf et al. (1939a, b; 1940). Excellent summaries may also be found in the writings of Sabin (1942), Callahan et al. (1946), and Schwartzman et al. (1948).

In man the disease has been described in four more or less distinct forms which vary with the age of the patient. The first is an infection affecting the foetus and the newborn child; this, the congenital type of the disease, being relevant to the present paper, will be described in fuller detail later. The second form is recognized as an encephalitis affecting older children. The third form shows itself as an acute febrile exanthematic illness affecting adults. Finally, there is a mild and apparently symptomless type of infection which may be recognized only by finding specific antibodies in the blood, or by the patient's giving birth to an infected infant.

Congenital Toxoplasmosis

The clinical and laboratory findings in this type of the disease are now becoming more clearly defined, and may be mentioned in the following categories:

1. Signs suggesting pathological changes in the central nervous system: tremor, spasticity, convulsions, microcephaly, hydrocephalus, mental retardation, and intracranial calcification.
2. Changes in the cerebrospinal fluid: xanthochromia, increase in protein, and pleocytosis, usually mononuclear.
3. Disorders of the eyes: ocular palsies, microphthalmos, vitreous opacities, and chorioretinitis affecting both eyes, especially in the macular region. Optic atrophy is found more rarely.
4. Demonstration of specific antibodies in the blood.
5. Isolation of the parasite from either the blood or other tissues.
6. Other occasional findings: anaemia, gastrointestinal symptoms, hepato-splenomegaly, pneumonitis, and myocarditis.

Pathology

Naturally occurring infections with this parasite have been found in a large number of animals, including cats, dogs, mice, rabbits, canaries, and sparrows. In animals infected either naturally or experimentally the disease is spread by the blood stream and most of the organs can be shown to contain parasites, though the brunt of the infection falls upon different viscera in the various species. Thus in the rabbit inoculated intracutaneously with virulent toxoplasma the brain is little affected, but in mice it is most commonly affected. In man it would appear that the distribution of the lesions depends upon the age of the subject, for in the adult the lungs seem specially liable to infection, though the liver, brain, myocardium, and other parts may also suffer. In the infant the central nervous

system is mainly involved, and the disease usually takes the form of diffuse encephalomyelitis. Focal, yellow lesions, varying from a few mm. in diameter up to 2 cm. have been described in the brain cortex, the basal ganglia, midbrain, pons, medulla, and spinal cord. Sometimes these are found in the walls of the intracerebral ventricles where the ependyma is lost. The meninges become thickened and adherent to the superficial cortical nodules. Microscopically these lesions show extensive necrosis of the nervous and glial tissues with cavitation and calcification. An area of tissue reaction occurs around the necrotic areas, and may be recognized by dilatation of the capillaries and an infiltration by plasma cells, lymphocytes, neutrophils, eosinophils, and macrophages. Fibroblasts from the capillaries of the brain or the overlying meninges may lead to the formation of granulation tissue, and adhesions may thus develop between the lesions and the meninges. More distant still from the centre of the lesion a glial and microglial reaction can be recognized. The infecting parasites can be found in large numbers at the margin of the necrotic areas and also in the meningeal exudate.

Almost identical changes are found in the retina, disrupting its various layers, and at times leading to granulation tissue which invades the vitreous humour. The choroid coat shows less involvement but is oedematous. The lesion does not affect the sclera, but may extend along the optic nerve. Maldevelopment of the eye such as microphthalmos would suggest that infection has occurred at an early stage of intra-uterine life.

Antibodies against toxoplasma may have been found in some infected animals and in man. They may be estimated by the neutralization test (Sabin, 1942), in which varying dilutions of a suspension of tissue infected with a virulent strain of toxoplasma and the unknown serum are injected intracutaneously into the back of a rabbit, and the resulting reaction measured. Complement fixation tests have also been used, but these have not been found very reliable. More recently an in vitro dye test for toxoplasma antibody has been developed (Sabin and Feldman, 1948).

Case Histories

Case 1. J.C. was prematurely born in the thirty-second week of pregnancy of a mother who had been well during the whole of her pregnancy. The delivery was described by her as a normal one, and the birth weight was 3 lb. 13 oz. Some cyanosis was noticed in the first three days of life, and the child was said to have been jaundiced from the fifth to the twelfth day.

The family history appeared to be a healthy one. The mother had suffered from chorea as a child. The father had been well all his life, and had served abroad during the 1939-45 war, visiting East and North Africa as well as Italy and France. There had been no previous children, and the mother had had no miscarriages. The home conditions were described as clean, and the only animal in the household was a dog. The blood of this animal as well as an excised lymph gland have so far failed to infect mice into which they were injected.

The child first attended the out-patient department at the age of thirteen weeks with a history of a feeding difficulty which had manifested itself as an excess of posseting. It was found, however, that, in spite of this sickness, he had gained 106 oz. since birth.

Examination revealed a rather pale-looking child with right sided microphthalmos (fig. 1) and obvious mental retardation. The skull measured fourteen and three-quarter inches in circumference, and there was an exaggerated Moro reflex to minor stimuli. No attempt was made to fix an object with the eyes, and the posture might have been regarded as normal for a child four weeks of age. There was slight stiffness of the lower limbs and a clonic response to the right knee jerk.

Examination of the eyes two weeks later revealed almost complete occlusion of the right pupil with posterior synechiae, and resolving areas of chorioretinitis with vitreous opacities. The left eye showed fewer synechiae but active choroidal infiltration of the nasal side of the fundus. Ten weeks later the eye lesions were described as settling down.

The child was admitted to hospital at the age of thirty-five weeks. The posseting had ceased within a few weeks of his first attendance, and the only complaint that the mother now had was that the child was unable to sit up, and that he did not appear to see very well.

Examination revealed very little that was new. He weighed 16 lb. 3 oz. The skull appeared even smaller than before in proportion to the rest of the body, and its circumference was 16¼ inches. The smallness of the frontal bones was particularly marked, there being a palpable and visible step down from the parietal to the frontal bones over the vertex. An estimate of the mental development according to the Gesell norms gave a rating of between sixteen and twenty weeks. There was marked hypertonicity of the lower limbs.

INVESTIGATIONS. A radiograph of the skull at the age of thirteen weeks revealed no abnormality. When it was repeated at the age of thirty-five weeks, small calcified areas about one to two mm. in diameter could be seen throughout the cortex, and a linear shadow in the region of the choroid plexuses (fig. 2). Air ventriculography showed a generalized dilatation of the ventricular system (fig. 3).

Serum of the mother and child was tested for toxoplasma antibody by Sabin in Cincinnati and was reported by him as unequivocally positive, the titre being 1 : 1024 in both sera, using the in vitro dye test (Sabin and Feldman, 1948). The father's serum gave a negative reaction. The cerebrospinal fluid of the child also contained the antibody in a titre of 1 : 16.

The maternal and child's blood Wassermann reactions were both negative.

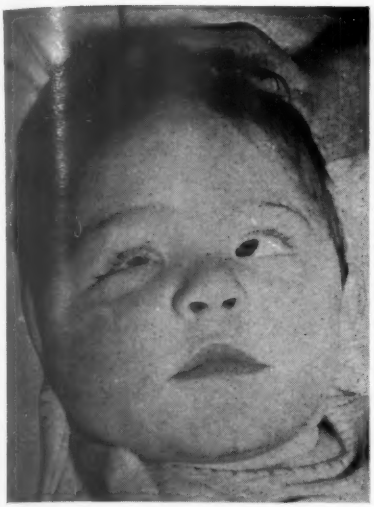

FIG. 1.

FIG. 1.—Case 1, showing facies and microphthalmos.

FIG. 2.—Case 1: calcified areas in cortex and linear shadow in region of choroid plexus.

FIG. 3.—Case 1: ventriculogram, showing generalized dilatation of ventricular system.

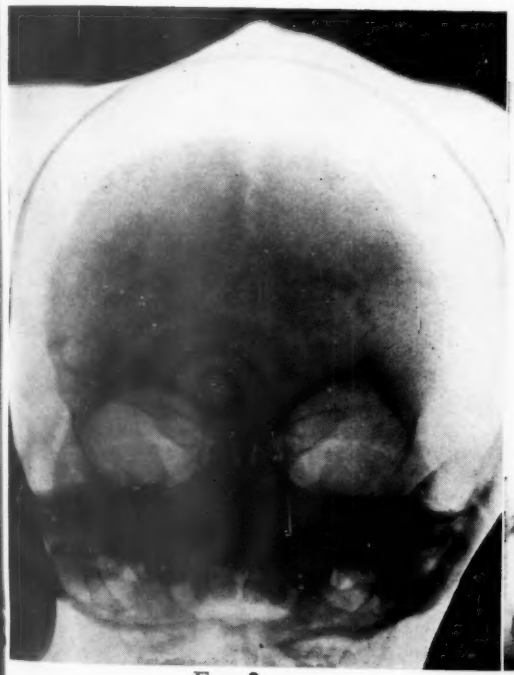

FIG. 2.

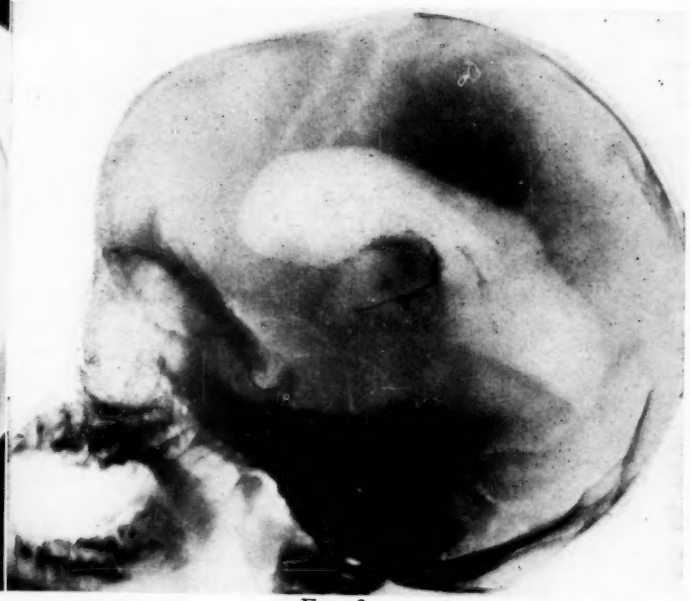

FIG. 3.

The child's blood showed moderately severe hypochromic anaemia, haemoglobin being 55 per cent. (alkaline haematin method 100 per cent. = 14·5 g. per cent.). Red blood cells numbered 4,800,000 per c.mm. of blood. The white blood corpuscles showed no abnormality in number or relative proportions. The anaemia, resistant to iron therapy, responded to a transfusion of 180 ml. of blood, and the haemoglobin rose to 90 per cent. and remained at that figure.

The cerebrospinal fluid was clear and showed no xanthochromia (cells 3 per c.mm.; protein 10 mg. per 100 ml.; chlorides 740 mg.; sugar 54 mg.; no parasites were found in a centrifuged specimen).

Material from the needle used in performing the ventriculogram was examined microscopically but no protozoa were found. It is not at present possible to proceed further with these investigations owing to lack of available animals.

No abnormality was found in the urine or stools at any time.

Examination of the mother revealed no clinical abnormality, and a radiograph of her chest showed no lesions suggestive of toxoplasmosis. Twelve

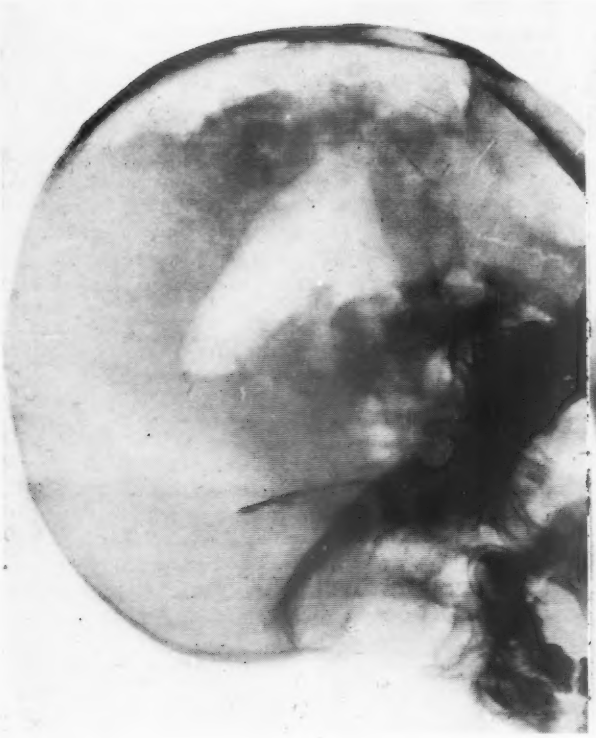

FIG. 4.

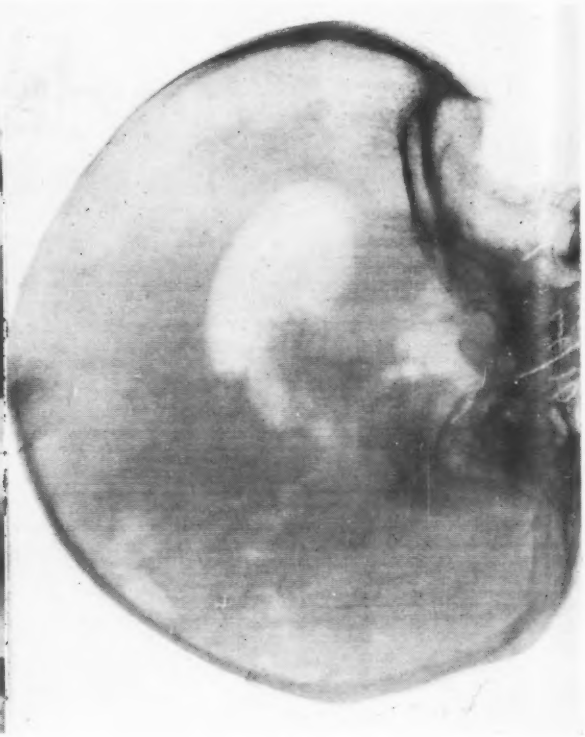

FIG. 5.

FIGS. 4 and 5.—Case 2: ventriculograms in prone position (fig. 4) and supine position (fig. 5), showing internal and external hydrocephalus.

days after having her blood taken for the estimation of toxoplasma antibody, and when five months pregnant, she had an abortion. Unfortunately we did not hear of this event until too late to obtain the specimen for examination.

Case 2. J.McC., a female infant, was born prematurely in the eighth month of pregnancy. At the twenty-sixth week of pregnancy the mother had an attack of what she called 'influenza.' This took the form of a pyrexial illness lasting a week in which the cervical lymph glands, and to a lesser extent those of the axillary and inguinal regions, became enlarged. Her doctor had described the illness as rubella without the rash. At the twenty-eighth week, according to the mother, external version was performed for a breech presentation. Delivery was described as normal and the birth weight was 5 lb. At the age of three weeks the child had a temporary gastro-intestinal upset which lead to vomiting and diarrhoea lasting for four days and which recurred slightly in a week's time. This disorder coincided with the cessation of breast feeding and the giving of sweetened condensed milk and barley water to the child.

FAMILY HISTORY. The mother appeared to have been in good health all her life. She had, however, had a miscarriage when ten weeks pregnant four years previously, and had one daughter who was well and who had had no serious illness. The father was discharged from the R.A.F. following recurrent synovitis in his knee after the removal of a cartilage. He had been in West Africa during his service. There had been a dog in the house during the pregnancy, and there were said to be large numbers of cockroaches and mice.

The child first attended the out-patient department at the age of ten weeks for persistent vomiting of her feeds. The bowels had been normal since the alimentary upset at the age of three weeks.

Examination revealed a pale and hypotonic child weighing 6 lb. 14 oz. The only other abnormalities found at this time were a slight enlargement of the liver and vertical nystagmus of slight degree. A simple change in the feeding technique was sufficient to cure the condition, and the child returned in a week's time having gained weight satisfactorily.

She was next seen at the age of thirty-seven weeks, when the mother complained that she was not sitting up, was unable to grip anything held in front of her, and could not take solid foods.

Examination showed that the child weighed 16 lb. 14 oz. and was markedly backward mentally.

Ophthalmic examination showed patches of choroidal degeneration in both eyes; in the right eye extending from the optic disc to the nasal side of the retina covering about one-sixth of the latter, and in the left eye extending on the temporal side of the disc over most of the retina, associated with much pigmentation and atrophy of the disc itself.

The child was admitted to hospital at the age of sixty-two weeks. The weight was now 18 lb., the incisor teeth had been cut, and the first molar teeth were just appearing. The mental retardation was still marked and according to the Gesell norms her developmental age was twenty-eight weeks. Sudden attacks of apparently causeless screaming occurred frequently but at no time did she show any convulsive tendency. The skull circumference was 15½ inches, and there was slight spasticity of all four limbs. The retinal lesions showed no change and no other abnormalities could be found in any system.

INVESTIGATIONS. A radiograph of the skull at the age of thirty-seven weeks had been reported as showing no calcification, but re-examination of this radiograph showed very slight and early changes of this kind. A repeat radiograph of the skull at the age of sixty-two weeks showed unmistakable calcification in the brain substance; there were multiple foci throughout the right parietal region of the brain, but these were too small (1-2 mm.) to reproduce in a photograph.

Air ventriculograms showed mild internal hydrocephalus but, as is best shown in the prone and supine films (figs. 4, 5), a marked external hydrocephalus was also present.

Serum reactions for toxoplasma antibody were investigated as before. The titre of the patient's serum was positive in a dilution of 1 : 4096, and that of both parents in 1 : 1024. The cerebrospinal fluid of the infant was positive in a dilution of only 1 : 4. The serum of the other child was unfortunately not reported upon.

The maternal and paternal blood Wassermann reactions were negative.

The child's blood showed mild hypochromic anaemia, the haemoglobin being 70 per cent. (alkaline haematin method 100 per cent.=14·5 g. per cent.), and the red cell count 4,400,00 per c.mm. of blood. The white cell count on admission showed a neutrophil leucocytosis, the total white cells numbering 34,000 per c.mm.; the polymorphonuclear cells numbered 20,000, lymphocytes 13,000, and monocytes 680. In two weeks' time the white cell count had become normal in all respects, and no cause for the previously high figure could be found. The haemoglobin remained at the same figure throughout.

The urine and stools were normal. The cerebrospinal fluid was clear, and contained 10 lymphocytes per c.mm., protein 20 mg. per 100 ml., chlorides 730 mg.; the sugar was not estimated.

Biopsy material from the brain needles used in the performance of the ventriculograms was examined microscopically with negative results. Animal inoculation with this material was not carried out.

The mother and older child were both examined clinically and radiologically and no abnormalities were discovered. The father was not examined.

Discussion

Though many of the criteria considered necessary for the diagnosis of congenital toxoplasmosis were present in the two cases which we have described, and the serum reactions were positive, yet it must be emphasized that up to the present time the parasite has not been isolated from these patients. It must be remembered, however, that isolation of the organism has proved to be difficult during the quiescent stage of the illness (Schwartzman et al., 1948); and as both our cases were probably quiescent at the time of testing, as shown by the extent of the calcification in the brain substance, the normal condition of the cerebrospinal fluid, and the inactivity of the ocular lesions, it is quite possible that even if we had been able to carry out animal inoculations our results might have been negative.

The significance of the serological tests for toxoplasmosis requires further consideration. The usual method, the neutralization test, demands a considerable amount of time, and, if large numbers are involved, a very great stock of animals. For this reason extensive studies do not appear to have been made. Callahan (1945) tested the sera of one hundred apparently normal people, seventy-seven of them being women between the ages of seventeen and twenty-four years, and twenty-three being men between the ages of twenty and twenty-eight years. He found the incidence of a positive neutralization test to be 2 per cent. in the whole group. Heidelman (1945), again using the neutralization test but with a selected group of patients, obtained the following results. Of twenty-seven patients with congenital toxoplasmosis, 63 per cent. were positive; of ninety-seven patients with anterior or posterior uveitis, 14 per cent. were positive; of nine patients with congenital chorioretinitis and other evidence of toxoplasmosis, 55 per cent. were positive; of seven mothers who had given birth to children with congenital chorioretinitis, six were positive. Of fifty-eight normal subjects, 10 per cent. had positive reactions. He concludes that between 10 and 14 per cent. of subjects without any evidence of toxoplasmosis as at present understood are found to have antibodies against toxoplasma in their blood, and he suggests that in some at least the antibody may be non-specific. This figure of 10 per cent. for the general population corresponds closely to the conclusions of Sabin and Ruchman (1942). Johnson et al. (1946), testing a selected series of thirty-two patients all with a central type of chorioretinitis, found that 62 per cent. had neutralizing antibodies in their sera.

From the above small number of cases it can be seen that a positive neutralization test does not necessarily imply that the patient is suffering from toxoplasmosis, nor, in our present state of knowledge, that he has ever had the infection. It is also clear from a study of the literature that the absence of a positive neutralization test does not exclude the diagnosis.

The serological tests in our two cases were performed by Dr. A. B. Sabin using a new technique that is to be published. We are not qualified to comment upon the details of this investigation, but Dr. Sabin's special experience of toxoplasmosis would seem to justify acceptance of his comment that the titres obtained were such as occurred only in proved recent cases of this infection.

Conclusions

It is probable that these two patients are suffering from congenital toxoplasmosis, and the finding of two such cases in one area within the period of six months raises the possibility that the condition may not be so rare as is at present believed. It would appear to us that the serological investigation of patients showing some or all of the manifestations of this disease, in particular mental retardation, microcephaly, and choroidoretinal degeneration in infancy, might well be extended in this country. An investigation of a cross-section of the population to determine the incidence of positive reactors and their further examination would be valuable.

Summary

Two cases showing the clinical manifestations of congenital toxoplasmosis have been described. Serum antibody reactions were positive, but the organism has not been isolated. It is suggested that the disease may be more frequent in this country than is at present believed, and that this possibility should be further investigated.

We wish to thank Prof. N. B. Capon for his valuable criticism and advice in the preparation of this paper; Dr. A. B. Sabin for his ready co-operation in the performance of the serological reactions; Drs. C. A. St. Hill, D. Mossman, and W. H. H. Andrews, for help in the pathological investigations; Mr. J. A. McCann for the ophthalmological reports; Mr. R. H. Hannah for the performance of the ventriculograms; and Dr. N. Walker for the radiological findings.

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OSTEOPETROSIS IN SUCCESSIVE GENERATIONS

BY

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Records of families in which osteopetrosis has appeared in successive generations are rare. The occurrence of the condition in mother and son is recorded in this paper.

Case Histories

Case 1. A full-term male child, weighing 6½ lb., the product of a second pregnancy, was born on Aug. 3, 1945. The parents were unrelated. When three months old the child was thought to be blind, and two months later on x-ray examination a diagnosis of osteopetrosis was made. Mental retardation was noted at ten months. At two years two months he was admitted to the Royal Blind School; he was a well built and well nourished child (fig. 1).

When two and a half years old he weighed 28 lb., was 33 in. tall, had a crown-rump measurement of 19½ in., and an arm span of 31 in. The intermeatal measurement was 12½ in., the occipito-frontal circumference 19¾ in. The thoracic circumference at the nipple level was 19 in. The head showed slight frontal and more marked parietal bossing. The general outline suggested a degree of hydrocephalus. The pupils did not react to light and there was bilateral optic atrophy. Nasal obstruction and mouth-breathing were present. Dental eruption had been normal and the teeth appeared in good condition, though the lower lateral incisors and lower right second molar were missing. No enlargement of liver, spleen, or lymph glands was present.

Blood examination showed erythrocytes 4,925,000 per c.mm. of blood; haemoglobin (Sahli) 95 per cent.; white blood corpuscles 12,500 per c.mm.; polymorphs: neutrophils 18·5 per cent.; eosinophils 1·5 per cent.; basket cells 4 per cent.; large lymphocytes 12·5 per cent.; small lymphocytes 57 per cent.; smear cells 4·5 per cent.; monocytes 2 per cent. No nucleated red cells or primitive white cells were seen.

Blood chemistry investigation gave a blood urea nitrogen of 17 mg. per 100 c.cm. of blood; serum calcium 10·2 to 11·8 mg.; inorganic phosphorus 4·1 to 4·4 mg.; phosphatase 8 units (King).

Radiographs of the skull and limbs showed the typical picture of osteopetrosis. In the skull (fig. 2) the anterior fontanelle was not completely closed and the suture lines were obvious. The increased density of the bones at the base of the skull was marked, as was the thickening of the posterior clinoid processes. The symmetrical nature of the condition was well demonstrated in radiographs of the limbs (figs. 3, 4, and 5). Clubbing of the lower end of the femur was typical. Comparison of figs. 4 and 5 shows that while there have been remissions in the sclerotic process at the distal end of the femur, there has been no accompanying remission in the clubbing. The humeri showed marked clubbing in the proximal thirds of the shafts.

When two years five months old the child showed evidence of pain and discomfort in the left forearm. Clinical examination, which disclosed the presence of some swelling, was resented. X-ray examination confirmed the diagnosis of a fracture of the left radius. No cause could be assigned in explanation of the injury. The fracture was situated in an area of sclerosis and showed no displacement. The arm was splinted and in twenty-four hours the child was using it freely. Callus formation was satisfactory (fig. 6). Six weeks later similar behaviour led to the discovery of a fracture of the right fibula. There was no displacement, and thirty-six hours after being x-rayed and having the leg splinted the child was observed to walk voluntarily. Callus formation was satisfactory. At this stage, the child was considered to be ineducable and was discharged from the Royal Blind School when two years eight months old.

Case 2. The mother of case 1 was the fifth child of healthy unrelated parents. She was born on Jan. 4, 1920. The condition was not suspected in her case until the diagnosis had been made in the case of her son. Her features and the shape of her head bore a striking resemblance to that of her child. There was no mental defect. Visual acuity was R. 6/6; L. 6/6. No enlargement of liver, spleen, or lymph glands was detected.

X-ray examination showed marked sclerosis of the basal skull bones with clubbed posterior clinoid processes. The suture lines were obvious (fig. 7). The humeri showed increased thickening of the proximal half of the shaft. The sclerotic areas were not sharply demarcated, but shaded off irregularly into areas of more normal bone (fig. 8). A radiograph of the pelvis was typical and disclosed that, as in case 1, there had been periods of remission in the sclerosing process (Fig. 9). There was no history of fractures.

No opportunity for further examination of this case was permitted.

Family history. The family relationships are shown in fig. 10.

No evidence of osteopetrosis has been found on x-ray examination of the parents of case 2, her husband, or the sibling of case 1. Among the siblings of case 2, the brother, born in 1915, had a broken leg while on war service. A radiograph of his leg at that time did not disclose any pathological factor. No further investigation of any member of the family has been permitted. It is stated that all the offspring of the siblings of case 2 are healthy. The sister, born in 1918, is said to bear a rather striking resemblance in stature and feature to case 2. No investigation of the family of the husband of case 2 has been possible.

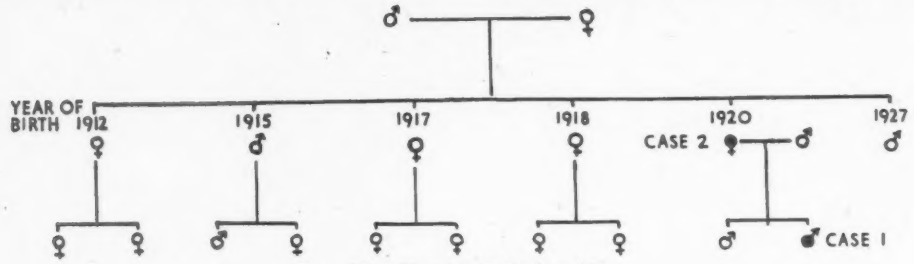

FIG. 10.—Family Relationships.

Discussion

Though it is forty-four years since Albers-Schönberg drew attention to this condition, the cause has not been discovered. Its occurrence has been recorded in Negroes and Asiatics as well as in the white races. Both sexes may be affected.

The condition has been diagnosed while the child was in utero (Pirie, 1930; Clifton et al., 1938; Jenkinson et al., 1943) and it has been diagnosed in late adult life (McPeak, 1936; Pagenstecker, 1935).

Studies of the pathology have established that there is a fault in osteogenesis, followed by a lack of osteoclastic activity. Osteoblasts are decreased in number and osteoclasts may be absent. The resultant picture is one of failure to resorb calcified cartilaginous matrix and remodel the primitive trabeculae. Both membranes and cartilaginous bones are involved in the distribution, which is symmetrical. The bone, though dense, is brittle and fractures easily; the term 'chalky bones' has been used to describe this. The fracture is situated in an area of sclerosed bone and is transverse. It heals without deformity (fig. 6). Dupont (1930) has suggested that the fracture occurs at an area of rarefaction interposed in the sclerosed bone. Unaffected portions of the skeleton may show osteoporosis. Abnormal modelling of bone is manifest in the form of clubbing. This is seen most readily in the posterior clinoid processes, the distal end of the femur, and the proximal end of the humerus. The clubbing is not related to sclerosis since it may persist when the sclerosing process has shown remission (compare figs. 4 and 5). The converse is also true, that sclerosis may be present without manifestations of clubbing. Pirie (1930) states that while clubbing is usually symmetrical it is not necessarily so.

The diploic structure of membranous bone is absent (fig. 2). It would appear that stimulus to growth of brain continues though the capacity of the skull does not keep pace with it. Some increased intracranial tension must result. The various foramina leading out of the skull are narrowed by the excessive deposit of bone. In the case of the optic foramen this has been demonstrated radiologically by Vidgoff and Bracher (1940) and Clifton et al. (1938) and at autopsy by Lorey and Reye (1923), Krause and Walter (1925), and Alter et al. (1931). It is probable that the narrowing of the optic foramina causes some obstruction to the venous return from the eyes so leading to papill-oedema and subsequent optic atrophy. A similar mechanism is suggested by Higinbotham and Alexander (1941) to explain the occurrence of hydrocephalus. Narrowing of the facial nerve canal may produce deafness. Gradual replacement of the marrow space by bone has been usually accepted in explanation of the blood dyscrasia with accompanying hepato-splenomegaly which is characteristic of the so-called malignant type. More recently, it has been suggested that in cases showing blood dyscrasia the primary defect is in the mesenchyme, which is the precursor of both osteoblastic and marrow tissues.

Imperfect or delayed dentition is said to be common. This is not so in either of the cases now recorded; and Vidgoff and Bracher (1940) report the presence of two teeth at birth.

The blood picture, when abnormal, is that of progressive anaemia accompanied by hepato-splenomegaly. Blood platelets remain normal in number, and bleeding, clotting, and fragility tests are unaffected. Studies of blood calcium and phosphorus have shown that there is seldom a departure from normal figures (case 1).

The idea that parathyroid dysfunction may play a part in the etiology of osteopetrosis should not be lightly discarded. While investigating the response of rats to daily injections of parathyroid hormone, Pugsley (1932) found there was first an increase in calcium excretion for four days. This was followed by normal or subnormal excretion of calcium,

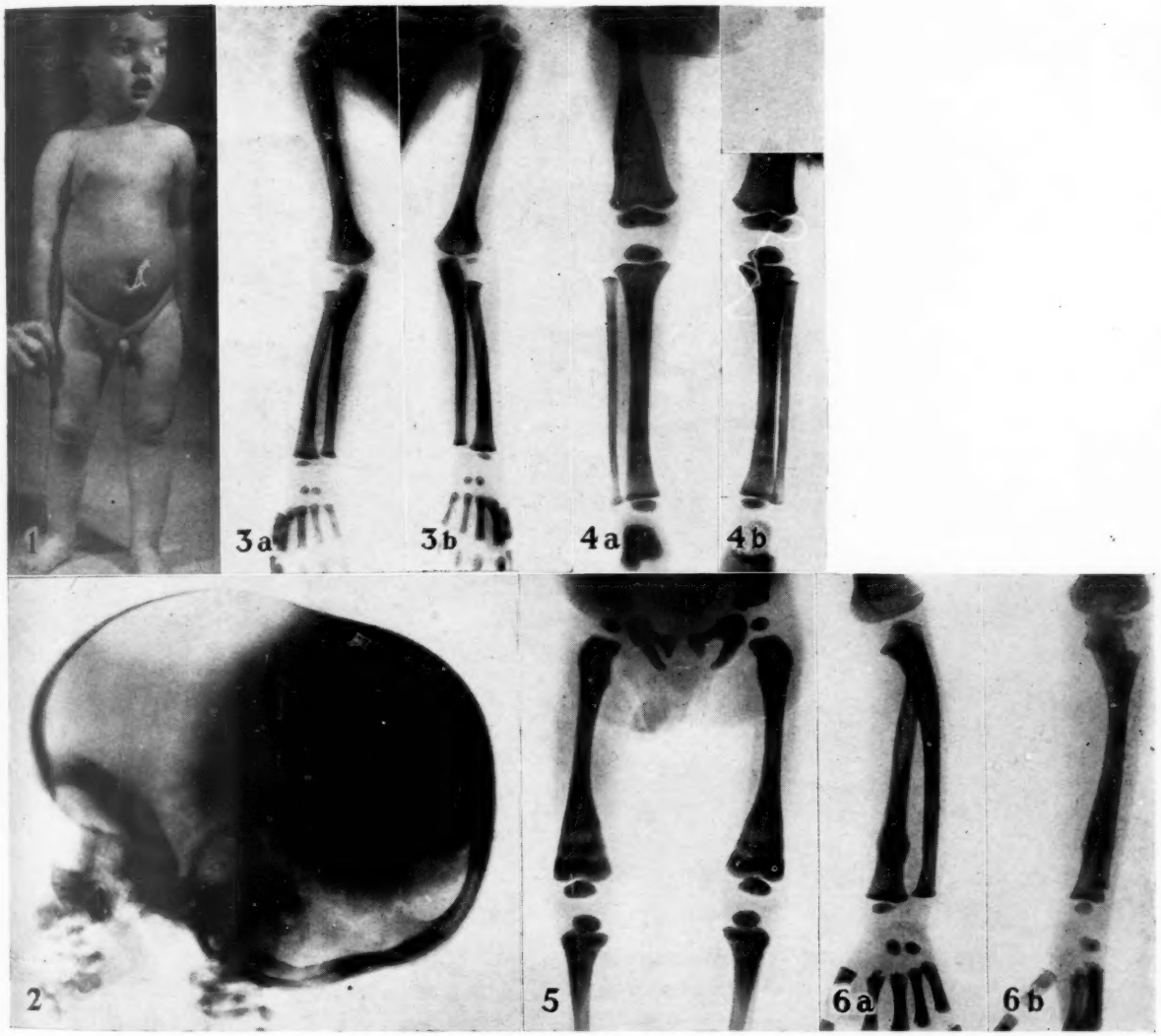

FIG. 1.—Case 1.—(Figs. 1 to 4 were all taken at 2 years and 2 months.)

FIG. 2.—Case 1. Note open anterior fontanelle.

FIG. 3.—Case 1, showing symmetrical distribution in upper limbs.

FIG. 4.—Case 1, showing symmetrical distribution and clubbing of lower end of femur. Note the remissions and their symmetry.

FIG. 5.—Case 1 at 9½ months, showing marked clubbing of the femora. Compare Fig. 4.

FIG. 6.—Case 1 at 2½ years, showing fracture of radius four weeks after its occurrence.

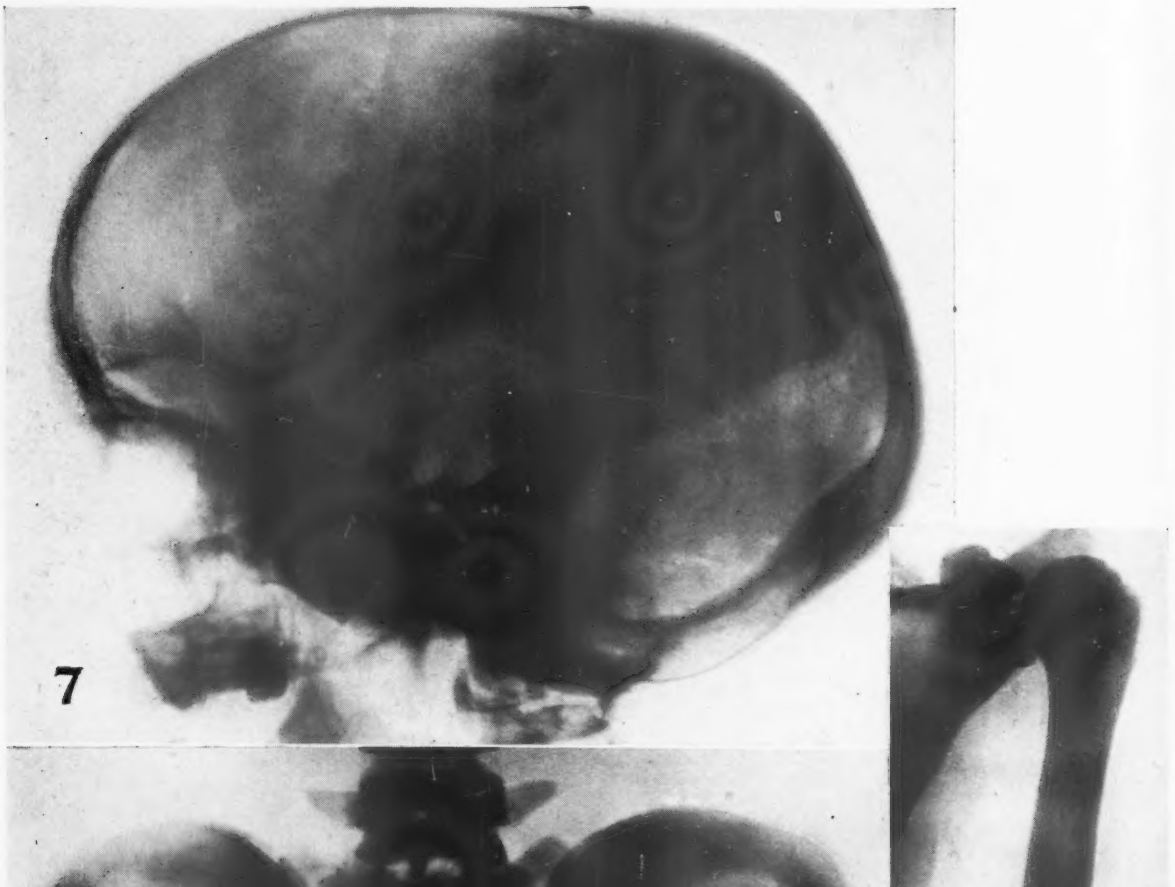

FIG. 7.—Case 2, aged 27 years, showing marked clubbing of the posterior clinoid process and well defined suture lines.

FIG. 8.—Case 2, showing abnormal modelling of the humerus.

FIG. 9.—Case 2, showing symmetrical distribution in the pelvis. The patient has had two normal full-term deliveries.

despite the continuation of the parathyroid hormone injections. Selye (1932) noted that following upon the acquirement of resistance to experimental hyperparathyroidism, if the administration of parathyroid hormone were continued proliferation of osteoblasts occurred and a condition resembling osteopetrosis was produced. This osteoblastic reaction occurs at the same time as the experimentally induced hypercalcaemia and the increased calcium excretion return to normal (Pugsley and Selye, 1933). Ellis (1934) administered parathormone to two cases of osteopetrosis, and obtained a hypercalcaemia which reached its maximum in ten to nineteen days. This was followed by a rapid fall in the blood calcium, although the administration of parathormone was not stopped. This type of response to parathormone in cases of osteopetrosis might be explained by the patient being in a period of remission when the observations were made. The two cases now reported confirm that periods of remission do occur in this disease.

McPeak (1936) and Harnapp (1937) divide osteopetrosis into two groups: one of severe or malignant cases, and another of mild or benign cases. When this is done, it is seen that, so far as data are available in the recorded cases, parental consanguinity is frequent in the malignant group and infrequent in the mild group.

Nussey (1938) has shown that the frequency with which osteopetrosis is associated with parental consanguinity is much greater than the frequency of consanguineous marriages in the community. He suggests that the malignant group is an inherited recessive defect, and that the benign group is an inherited dominant defect. In accepting this grouping it should be kept in mind that in 60 per cent. of the recorded cases and in 66 per cent. of the families concerned it is not stated whether there was, or was not, a blood relationship between the parents.

In a great many instances there has been no radiological survey of the family. Pagenstecker (1935), for example, records the condition in a father and son. He obtained these two cases by chance, the father and son coming to him on different occasions for radiological examination. He did not investigate the family.

A survey of the literature shows that up to the present time eight instances of the occurrence of osteopetrosis in successive generations have been recorded. In arriving at this total the paper by Lauterburg (1926), quoted by Nussey (1938), has been excluded. Reference to this article shows that the two cases recorded were brothers, and not cases occurring in successive generations as stated by Nussey. The reference which Nussey should have given, but does not give, is Lauterburg (1931). The first record is by Ghormley (1922), who reported the condition in father and son; Lauterburg (1931) and Pagenstecher (1935) also reported it in father and son. Pirie (1930) recorded the condition in a mother and three of her children. The appearance of osteopetrosis in three successive generations is recorded by McPeak (1936). The cases were a woman, two of her daughters, and three granddaughters and two grandsons, all by one of these daughters. Zaleski (1932) records the condition in father and daughter. Harnapp (1937) noted an instance of the condition in a man, his two sons, and three of his five daughters. His two siblings were healthy and his parents healthy and unrelated. He was not related to his wife, who was seven months pregnant. Her unborn child was considered to be radiologically normal. Winter (1945) records osteopetrosis in an eighteen-year-old male and his fifty-five-year-old mother. In neither of these cases were the parents related.

Apart from Harnapp and Winter, none of these authors state whether or not there was parental consanguinity.

The cases reported by Pirie appear to have been of a benign type, though assessment is somewhat vitiated by a family history of diabetes for three generations. McPeak's cases are all considered to be benign, there being no blood dyscrasia, blindness, deafness, or mental defect, though fractures were present in some instances. The cases reported by Ghormley, Pagenstecher, Lauterburg, Zaleski, Harnapp and Winter all appear to be benign and showed no mental defect or optic atrophy.

While this is strong evidence in favour of a division into a malignant inherited recessive type and a benign inherited dominant type, it may be doubted whether the present cases can be so easily grouped. The mother of case 1 may be considered to show the condition in a benign form, but there is doubt about classifying the child as a benign case. Absence of blood dyscrasia and the tendency towards remission of the osteo-pathology shown by comparison of figs. 4 and 5 can be accepted as evidence of benignity. Against this must be set the presence of optic atrophy, mental defect, and the occurrence of fractures.

This is the first occasion on which optic atrophy and mental defect have been recorded in a case of osteopetrosis in the second generation, and it may be advisable to wait a year or two before finally classifying this case.

Summary

1. Osteopetrosis occurring in a mother and son is recorded.

2. The occurrence of fractures, optic atrophy, and mental defect in osteopetrosis in the second generation is recorded for the first time.

3. There are eight records of osteopetrosis in successive generations in addition to that now recorded.

4. The investigation of osteopetrosis should always include a statement of the family relationships and radiological examinations of parents and siblings if practicable.

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GANGRENE AND THROMBOSIS IN AN INFANT WITH CONGENITAL HEART DISEASE

BY

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Only some fifty cases of gangrene in infants have been recorded in the literature, and the vast majority of these have occurred in the neonatal period (Dohan, 1934). The onset of gangrene after this period may be in association with severe infections (Watkins, 1938) or congenital heart disease (Gross, 1945). Current interest in cyanotic congenital heart disease warrants recording a case with this rare, but possibly preventable, complication.

Case Report

The patient, a male infant aged ten weeks, was admitted to hospital with a history of dark coloration of his left foot for four days, and of the right foot for one day.

He was born by breech delivery (birth weight 7 lb.) following a full-term normal pregnancy. Both parents and six siblings, including a twin sister, were healthy.

He had been cyanosed from birth, and was first seen in the out-patient department at the age of one month when it was noted that he had an enlarged heart and a harsh systolic murmur over the whole praecordium. The cyanosis was uniform and crying made the child breathless, but there was no evidence of congestive failure.

An accurate diagnosis of the congenital heart lesion was not attempted at this time, and he was seen at regular intervals up to the age of seven weeks. The general condition remained good but there was a failure to gain weight in spite of an adequate caloric intake.

For five days before the onset of the change in the feet the baby had been reluctant with his feeds. His mother stated that he was feverish during this time. He was, however, again feeding normally when admitted.

Examination. The weight was 6 lb. 12 oz., and the rectal temperature 97·4° F. The child was generally cyanosed and fretful but not dehydrated. Well demarcated gangrene of the feet (figs. 1 and 2) was present, and there was slight pitting oedema of the hands and of the legs below the knees. The arms were held in flexion, and there was a marked increase in muscular tone throughout the body.

Cardiovascular system. Pulsation could be felt in both femoral arteries but was not detected in the popliteals. There was no distension of the veins in the neck. The pulse rate was 150 per minute and was regular. The heart showed enlargement clinically, and the systolic murmur had remained unchanged.

No abnormality was found in the lungs, abdomen, or central nervous system, and there was no evidence of infection.

Investigations. The red blood cells numbered 6,000,000 per c.mm. of blood (haemoglobin 14 g. per cent.), and the white cells 6,500 per c.mm. (polymorphs 47 per cent., lymphocytes 42 per cent., monocytes 1 per cent.).

The urine was normal and blood culture negative.

A radiograph of the chest (Dr. Lodge) showed generalized enlargement of the heart. The vascular pedicle was small. The appearance was suggestive of transposition of the great vessels (fig. 3).

In view of the poor prognosis no specific therapy was undertaken. The child gradually became more apathetic and prone to dyspnoeic attacks. Oedema of the limbs spread to the trunk, but there was no extension of the gangrene. Death took place on the thirteenth day after admission.

Post-mortem report. There was oedema of the legs, sacrum and back, as high as the tenth rib, with gangrene of both feet as seen clinically.

The heart was enlarged, the right auricle being approximately twice the size of the left. There was transposition of the aorta and pulmonary artery. There was no endocarditis. The ductus arteriosus and foramen ovale were patent. There was thrombosis of the inferior vena-cava as high as the renal veins, in the internal iliac veins, and down to below the knees into the gangrenous areas. Several small vessels over the surface of the brain were thrombosed and the choroid plexus on both sides was grossly distended and thrombosed. The internal iliac and femoral arteries were patent and no arterial thrombosis was noted other than that in the popliteal arteries.

The respiratory and alimentary tracts, liver, spleen, pancreas, kidneys, adrenals, thymus, thyroid, lymph glands, and bones were normal.

Histology. In the lung some alveoli were collapsed, and many cells contained fat globules. The brain showed degeneration with many Hortega cells, and thrombosis in the vessels of the choroid

plexus. The blood vessels showed no change in structure; the intima appearing to be normal. Thrombus in some of the veins of the leg showed early organization.

Histology of the liver, kidneys, pancreas, and umbilicus showed no remarkable changes.

Discussion

Embolism and local disease of the blood vessels are unlikely causes of the gangrene in this case in view of the findings. Peripheral vasoconstriction, which may occur in states of severe heart failure (Fishberg, 1938), is a possible mechanism, but there is no evidence in favour of this.

The main feature at necropsy was the thrombosis, which affected (1) the vessels of the lower limbs extending in the case of the veins as high as the inferior vena cava, and (2) the choroid plexus and vessels over the surface of the brain. This wide distribution suggests that some general factor was responsible.

Thrombosis is a complication of cyanotic congenital heart disease and it is particularly prone to occur when polycythaemia becomes extreme, as in dehydration (Taussig, 1947).

The onset of gangrene here coincided with a period when fluid intake had been low for several days, and it seems probable that thrombus formation at this time occluded the blood supply to the feet. This would support the contention that every effort should be made to avoid dehydration in children with cyanotic congenital heart disease.

Summary

A case of gangrene of the feet in an infant aged ten weeks with cyanotic congenital heart disease is described. The possible causes leading to this complication are discussed.

I am indebted to Dr. J. L. Emery for the post-mortem report, to Dr. T. Colver for allowing me to publish this case, and to Prof. E. J. Wayne for his advice and criticism.

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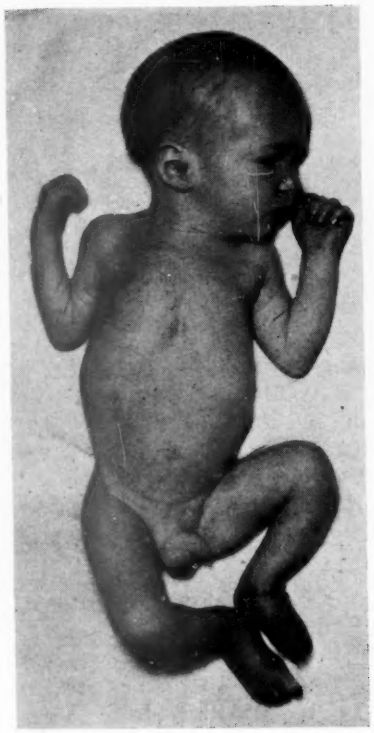

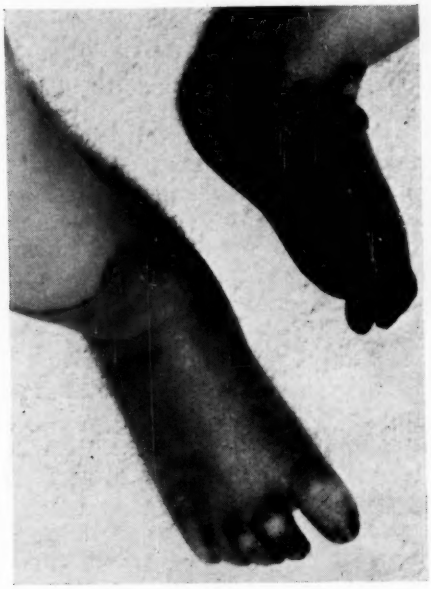

FIGS. 1 and 2.—Photographs showing gangrene of the feet.

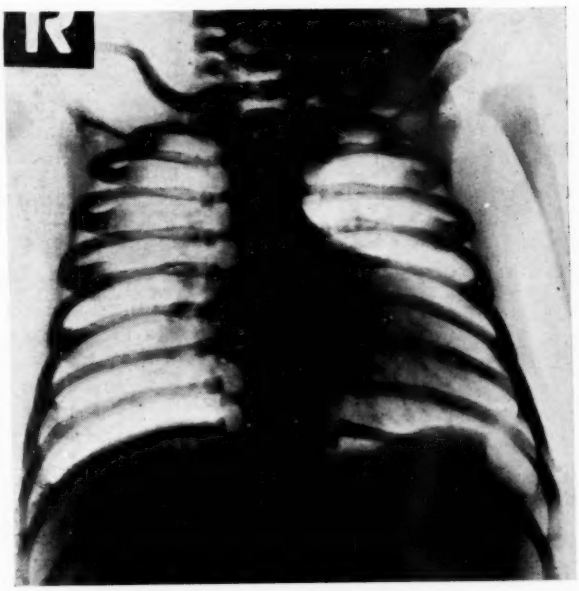

FIG. 3.—Chest radiograph.

GANGRENE IN CONGENITAL SYPHILIS

BY

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Peripheral circulatory disorder in early childhood is somewhat unusual except as a temporary disturbance consequent upon capillary stagnation, coldness, or other simple reversible phenomena. The occurrence of ischaemic disorder sufficient to evoke gangrenous changes is not only rare, but is clinically striking and necessitates an urgent approach to the etiology.

Acute arteritis may occur during or subsequent to severe infection. Such arterial changes have been recorded in the enteric fevers, typhoid fever, scarlet fever, and diphtheria. In the newborn, general or umbilical sepsis has been related to acute arterial ischaemic necrosis, especially in the limbs. In most examples the terminal branches of the limb circulatory system have become variably affected with arterial thrombosis to an extent sufficient to precipitate rapid necrosis of even a hand or a foot. Under these circumstances it is reasonable to suppose that the arterial walls have succumbed to a focal nodular, or more diffuse, necrotizing arteritis, and sudden massive endarterial occlusion has supervened. In some cases arterial embolism may be the operative cause, but this is much less likely in view of the wide lability of possible collateral routes of blood supply of the limbs in the young child.

Many of the clinical effects of infection with the Treponema pallidum are related to the endarterial changes in the individual focal lesions, especially in the acquired forms of syphilis. One of the outstanding features of congenital syphilis, however, is the peculiar insusceptibility of the cardiovascular system and a relative immunity of the arterial structures to direct disease or degeneration. It has, however, been occasionally observed that ischaemic effects, with in some cases an extension to tissue necrosis, may take place and are more usual in the young child. Illustrated examples of this condition appear in the works of Stokes (1944), and Pritchard (1938). Others have noted an occasional clinical relationship between congenital syphilis, peripheral arterial disease, and paroxysmal haemoglobinuria: in such a group disorder the phasic haemoglobinuria may arise proportionately to the cooling effect and local circulatory stagnation consequent upon the syphilitic endarterial disease.

Whilst it must be recognized that vascular lesions of such severity are only remotely probable, the example recorded here is of special interest in view of the extensive and crippling damage which ensued and of the rapid and satisfactory remedial effects obtained in some peripheral areas which were threatened with gross destructive changes.

Case History

A.B., aged 2 years, was the second child in the family. The first child, a boy aged 7 years, was healthy and had a negative Wassermann test. A third child died at the age of 1 month from alleged bronchopneumonia. The parents appeared to be well and gave no history of syphilitic lesions.

A.B. first came under medical observation in hospital on Feb. 18, 1948, at the age of 14 months. He was a full-term infant of normal delivery and appearance, but there was a history of a rash on the nates and some troublesome rhinitis during the earlier weeks of life. Progress had not been satisfactory, and admission to a regional hospital was sought because the baby was miserable, listless, and of inadequate weight. The admitting physician noted that there were some clinical features of unusual significance, and a special record was made in regard to rhinitis, some ' bossing ' of the frontal region of the head, and a rash irregularly disposed over the face and buttocks. The skin was generally dry and the hair sparse. There was no evidence of any visceral abnormality and the spleen and liver were not enlarged. The nervous system, including the eyes and hearing, was normal. The right hand was cyanosed and oedematous, and the tips of the second and third fingers were discoloured and tender. On the left hand the tips of the third, fourth, and fifth fingers were blue and tender (fig. 1). The right foot showed a necrotic area on the dorsum and the fourth toe was discoloured, but these variably affected areas were not recognizably cold to touch (fig. 2). Careful examination failed to reveal any significant reduction in pulsation of the radial and dorsalis pedis arteries on either side. During the following week the darkening discolouration of the fingers, especially of the larger part of the right hand (fig. 3), became suggestive of a gangrenous transformation, and the affected parts

failed at any time, even under conditions of applied warmth, to improve. Vasodilator drugs also failed to relieve the local circulatory disturbance. It was noted that the affected areas were warmer to palpation than their appearance indicated. As a means of forestalling secondary sepsis, a course of sodium penicillin (50,000 units six-hourly intramuscularly) was begun. The right hand remained darkened and became very swollen and it appeared that a red line of demarcation was developing. Amputation was suggested, but this was considered unwise owing to the poor general condition of the child. Shortly afterwards the child's blood Wassermann reaction was reported strongly positive, and the same result was obtained in both parents. In view of this, penicillin was continued and was augmented by injections of bismuth (0·25 ml. daily) and suitable doses of potassium iodide and liquor hydrarg. perchlor. The child improved clinically during the following few weeks, but unfortunately the nutritional state of the right hand failed to improve proportionally. In fact dry gangrene supervened, with its limitations at the more defined line of demarcation. However, it seemed clear that the active gangrenous zone was considerably smaller than had appeared probable at an earlier date, especially before the commencement of urgent and intensive anti-specific therapy. It is of some interest that after the beginning of penicillin treatment the child had had fever reaching to 103° F.

A month later, during which time there had been difficulties about continuity of treatment and dangers had again arisen in regard to the gangrenous areas, the child entered the Bristol Children's Hospital on Feb. 22, 1948.

The outstanding clinical features at this admission were the characteristic 'special facies' with suspicious perioral scarring and a conspicuous facial profile. The dry gangrene of the right hand was sharply demarcated at the level of the proximal third of the metacarpus (fig. 4). The third, fourth, and fifth fingers of the left hand were plum-coloured, except for their tips which were quite black, and the nails appeared to be necrotic. The terminal phalanx on the fourth right toe was similarly blackened and the nail necrosed. No appreciable reduction of pulsation in the peripheral arteries could be detected. X-ray examination of the whole skeleton revealed an advanced and extensive degree of syphilitic osteo-periostitis with involvement of the tibial, femoral, and ulnar bones. Treatment with penicillin was again begun (60,000 units three-hourly). On no occasion was haemoglobinuria detected, and the urine was repeatedly normal.

After one week's intensive penicillin treatment it was decided by Prof. R. Milnes-Walker that there was no alternative to amputation of the gangrenous portion of the right hand, and on March 30, 1948, this was carried out at the level of the metacarpo-phalangeal joint of the thumb and the metacarpal line of the remaining parts of the hand. At this time the child's general condition, especially the nasal infection, had considerably improved. Progress in the amputated area was satisfactory (fig. 5). A small eschar separated from the right fourth toe and the discoloured necrotic areas on the left hand showed corresponding marked improvement. The necrotic nails had separated. Two weeks after the surgical treatment the amputation area was granulating and healing satisfactorily. A course of three weeks' penicillin treatment was concluded. The blood Wassermann and Kahn reactions remained positive. Continuity of therapy was maintained by injections of sulpharsenobenzine as 'sulphostab' 0·01 g. weekly and bismuth 0·01 g. bi-weekly. It was clear that the anti-syphilitic treatment was proving effective, and excellent general improvement was apparent in nutrition, mental and physical activity, and a restoration of normal rate of growth.

On no occasion had the cerebrospinal fluid shown any abnormality, and it was perhaps remarkable, in view of the severe general infection, that the fluid's Wassermann reaction and the colloidal gold curves were normal.

Careful and continuous chemotherapy was maintained in the Children's Hospital over a period of twelve weeks. In the final period all signs of active disease had cleared and the Wassermann reaction became negative. Suitable continuity of treatment in the out-patient department was maintained.

Discussion

Peripheral vascular changes resulting in gangrene in a case of syphilis present, according to Stokes (1944) and other writers, little that is characteristic of syphilis. However, it is generally assumed that where the condition occurs in the presence of florid manifestations of syphilis this disease is responsible for the vascular changes which precede occlusion.

The possible causes of peripheral gangrene occurring in childhood are much less numerous than in adults. In adults many diseases must be excluded before syphilis can be diagnosed.

In both adults and children the only infallible method of ensuring the veracity of such a diagnosis would be the demonstration of the Treponema pallidum in the affected tissues. The literature does not afford very conclusive evidence that this has been done in the case of peripheral lesions. However, Warthin (1922) claimed to have found spirochaetes in popliteal and tibial arteries in symmetrical gangrene simulating Raynaud's disease.

In the case here reported, on the score of age, arteriosclerosis and von Buerger's disease could be eliminated as causes. From the history there was nothing to suggest a traumatic or toxic origin. Clinical findings in the child included a normal urine, and no evidence of cardiac abnormality. Diabetes and arterial embolism could also be excluded. Periarteritis nodosa, Raynaud's disease, and syphilis remained as possible causes.

Periarteritis nodosa may affect individuals of all ages, and the condition has been observed in infancy. Those cases which have shown digital gangrene from

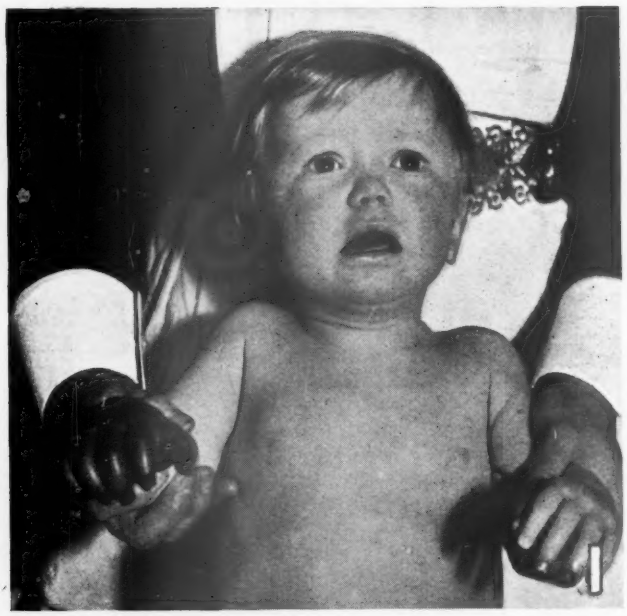

FIG. 1.—Condition shortly after admission (Feb. 18, 1948) showing facies and gangrene of hands. The photograph was taken on Feb. 25.

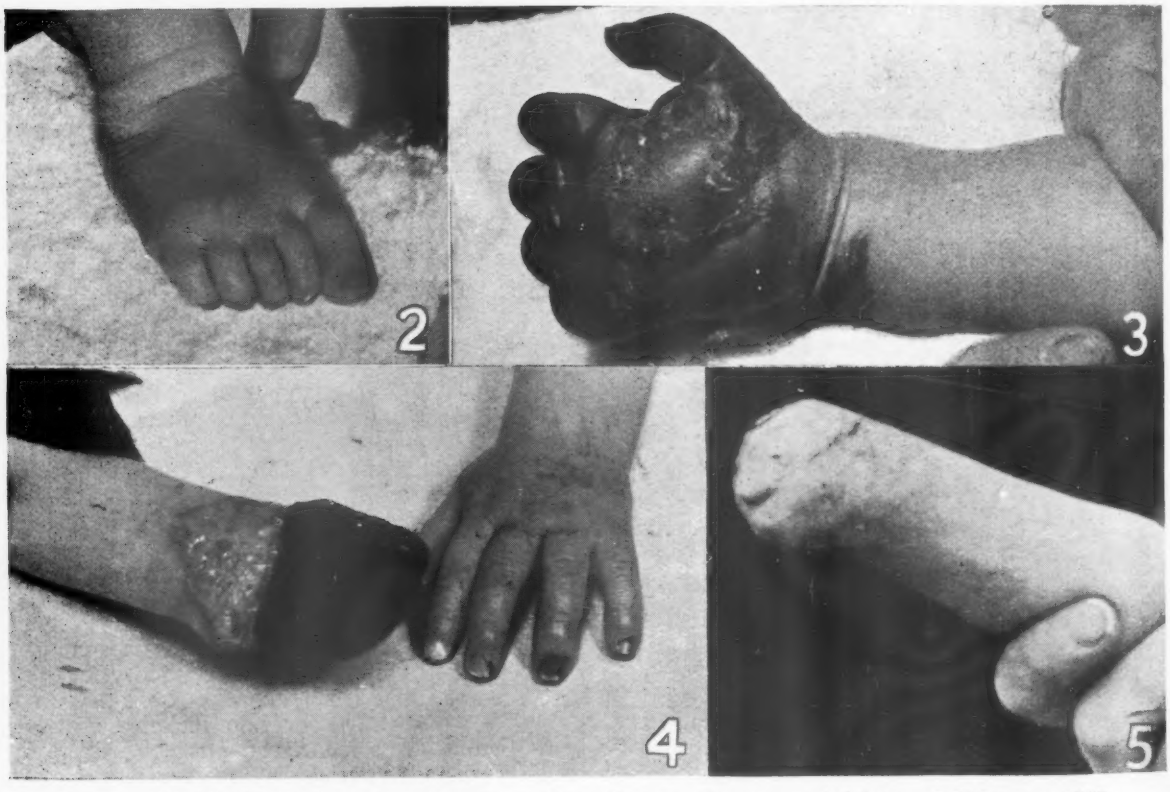

FIG. 2.—The right foot, showing necrotic area on the dorsum (Feb. 25).

FIG. 3.—Gangrene of right hand, February, 1948.

FIG. 4.—Hands, March 25, 1948, after the first course of penicillin. Note the line of demarcation of the gangrenous area.

FIG. 5.—Right upper limb one month later after excision-amputation of necrotic tissue (March 30).

thrombotic occlusion of the peripheral arteries have also shown other constitutional effects and more widespread lesions. The more general symptoms and signs associated with periarteritis nodosa were noticeably absent in this case.

Raynaud's vascular disorder may occur at any age but is quite uncommon before puberty, and in order to constitute the clinical diagnosis the following criteria are usually required: (1) intermittent attacks of cyanosis and digital pallor, influenced by cold and emotion, the affected parts subsequently recovering with hyperaemia; (2) little or no change in the peripheral arterial pulses; (3) gangrene never presents at the first attack, and if it occurs is usually slight and confined to small areas only.

The case now discussed cannot be said to conform entirely to all of these criteria; indeed it is only in the matter, albeit an important one, of continued presence of arterial pulses that there is a resemblance to the Raynaud syndrome.

There exists a group of conditions in which paroxysmal digital cyanosis occurs to which the term 'Raynaud's phenomenon' is better applied. In such conditions the paroxysm is considered to be secondary to other bodily disease. There may be such digital cyanosis, sometimes progressing to gangrene, occurring during exposure to cold. Paroxysmal haemoglobinuria and, more rarely, severe urticarial phenomena, may be associated. This condition has been described with congenital syphilis in childhood. It is supposed that chilling of the endothelial cells of the smallest blood vessels favours arteriolar thrombosis in the parts affected. Where syphilis is present energetic anti-syphilitic treatment offers a prospect of recovery.

The case described here showed no evidence of urticaria on exposure to cold, and paroxysmal haemoglobinuria was not an apparent feature.

Where the effect of cold cannot be incriminated, then it is necessary to consider a syphilitic process as the cause of damage to the arterial wall. Syphilis may produce a panarteritis of which intimal hyperplasia is a principal feature. If this is sufficiently severe the circulation will be locally reduced and thrombosis may be expected. Possibly there is an initial period of peripheral ischaemia related to a reflex vasospastic response in the local inflammation. On such a hypothesis one might explain some of the beneficial effects of specific treatment in these cases.

Heller and Alvari (1941), in reviewing gangrene of the extremities in the newborn, assembled forty cases from the literature. Of these they were able to identify those due to pressure associated with difficult labour, those due to infection, and a number of cases vaguely attributed by the authors to 'Raynaud's disease' or neurological disorder. They advanced an ingenious theory of temporary agglutination of the intimal surfaces of the smaller arteries, in which fibrin sealed the surfaces together but in which thrombosis formation did not necessarily occur. Removal of pressure or spasm would allow the pulsating proximal blood column to wedge open the sealed walls and so restore the circulation before an irreversible change occurred. These authors plead for delay of amputation in such cases to see if there might be any improvement.

Sections of the excised necrotic tissue revealed no change in the vascular walls that could be said to be characteristic of syphilis. This would agree with Stokes's experience. There was no evidence of any gummatous change in the vessel walls; such changes have, however, been recorded in adults with acquired specific disease.

In adults gangrene of the extremities is sometimes seen after acute infections, especially in the tropics. Bloss (1948) described such a case in an African, and referred to articles by Gelfand (1947) and Salter (1947), who have reported six cases, four of whom also had syphilis. A similar example was seen by one of us in Abyssinia. This patient had an acute attack of malaria and had syphilis as well. It would seem that syphilitic disease may well be a dominant factor in gangrene of the extremities following acute intercurrent disease.

In children and young adults bilateral gangrene of the extremities has been observed in the absence of obvious cause in apparently healthy individuals. More often there is a history of acute infection or preceding malnutrition. In such cases the changes in the affected parts is acute and proceeds quickly in the course of a few days. Some recovery, however, is usual, and the ultimate area of gangrene may be less than was originally threatened. The ears and nose may also be affected. Exposure to cold may not necessarily be an aggravating factor, and the parts are uninfluenced by heating. The pulses usually remain normal. It is interesting to note that Raynaud himself observed such a case. This was a boy of $3\frac{1}{2}$ years, in whom the circulatory and tissue changes were attributed to emaciation.

Von Khantz (quoted by Heller and Alvari, 1941), in reporting fifty cases of gangrene of the extremities in childhood, attributed thirty-nine of these to acute infection. The nature of known infections was distributed as follows: diphtheria 6; scarlet fever 8; measles 4; typhoid 6; syphilis 8; enteritis 4; typhus 3; pneumonia 2; omphalitis 2. Our case has much in common with the clinical picture seen in this series, and yet syphilis was present.

Congenital syphilis is well known as a cause of failure to thrive and of malnutrition. The child in question was certainly malnourished at the time of recognition of the syphilitic disease. The lesions and the general health of the child improved considerably with anti-syphilitic measures, and it would appear that the gangrene here was due to a devascularizing effect of syphilitic infection rather than to general malnutrition consequent upon congenital syphilis.

Anwyl-Davies, Nabarro, and Parkes Weber (1940) reported gangrene of the extremities in two sisters. The children were the daughters of a woman who was herself a congenital syphilitic. Both children, as infants, had gangrene of the identical digits of

the right hand. In both the lesions healed by scarring and tissue loss.

Treatment. Treatment with sodium penicillin initiated marked general improvement and obvious clinical retrogression of the local lesions. In the initial stages of the condition the child also received potassium iodide. The use of potassium iodide as a therapeutic test is, however, according to Stokes, of little value, as other vascular diseases besides those associated with syphilis may show some favourable response. The child received 50,000 units of sodium penicillin, six-hourly at first, to a total of 1,500,000 units. Subsequently he received a further course of 60,000 units three-hourly for sixteen days.

We must admit the possibility that the initial treatment with penicillin may have been somewhat inadequate. Tissue necrosis was already incipient when treatment was begun, but in view of the extent of recovery, particularly as regards the digits of the left hand, more heroic doses might have been given with advantage.

In cases where syphilis is suspected early, energetic treatment at the stage of primary discoloration may possibly produce a recovery without loss of tissue. Barker (1948), reviewing penicillin treatment of syphilis, considers that the course of penicillin given for the treatment of congenital syphilis in the past tended to be inadequate and of insufficient duration, and the relapse rate was unfortunately high. It appears that the minimum dose should be 20,000 units per lb. of body weight, given three-hourly for fifteen days. The optimum dose may be even larger and should be about 50,000 units in twenty-four hours per lb. of body weight, and given at three-hourly intervals. In forty to fifty per cent. of cases a reaction in the form of mild fever for two or three days may follow commencement of penicillin. Such a reaction was shown in this child. Gastro-intestinal disturbance may also occur in this phase of the therapy, but such reactions are rarely severe enough to justify any modification of the treatment.

Summary

An example of peripheral gangrene in a child under two years of age and suffering from congenital syphilis is described. Gangrene in the extremities in infancy and childhood is also briefly reviewed.

We are indebted to Prof. A. V. Neale for his interest in our paper and for his permission to use the clinical data. Dr. A. D. Fraser kindly reported upon the pathological examination of the excised tissue. We are grateful to the staff of the Dorset County Hospital for some of the earlier notes in the clinical history and for the photographs of the child.

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REVIEWS

Garrod, Batten, and Thursfield's Diseases of Children (Fourth Edition). Edited by DONALD PATERSON, M.D., F.R.C.P., Consulting Physician, Hospital for Sick Children, Great Ormond Street, and ALAN MONCREIFF, M.D., F.R.C.P., Nuffield Professor of Child Health, University of London. Vol. II. With contributions by twenty-four contributors. 1949. London: Edward Arnold and Company. Pp. 1033. (Price 40*s.*)

The second volume of this famous textbook has appeared after the first volume has already been reprinted. This alone should ensure the successor an immediate and hungry public. The subjects dealt with are organic and functional disorders of the nervous system; congenital mental defect; diseases of the eyes, muscles, bones, and joints; orthopaedic surgery; medical diseases and surgery of the urogenital system; diseases of the liver, peritoneum, skin, and cardiovascular system; rheumatism; blood disorders; infections and venereal diseases; and malignant disease in childhood. The first section (organic diseases of the nervous system) is of particular interest, since it represents a combined production by a physician and a neurosurgeon; it has been entirely re-written, providing a reminder, perhaps, that neurology is not the sterile and static academic discipline sometimes imagined. With such variety of subjects and authors represented, it need only be said of the second volume as a whole that it maintains the standard

set by its predecessor and completes what has been a popular British textbook for some thirty-six years.

The Child in Health and Disease. A Textbook for Students and Practitioners of Medicine. Edited by CLIFFORD G. GRULEE, M.D., Rush Professor of Pediatrics, University of Illinois; and R. CANNON ELEY, M.D., Associate in Pediatrics and Communicable Diseases, Harvard University Medical School. 1948. Baltimore: The Williams and Wilkins Company. Pp. 1066.

With seventy-five contributors represented within the covers of a single volume, this is a work which might well have appeared as a system of paediatrics in the more spacious days of publishing. The single-volume format, however, has much to recommend it, and although it has taken several years to produce, the editors are to be congratulated on the addition of an up-to-date and authoritative contribution to the literature. It would be impossible to attain a uniform standard throughout a work of this type, and different authors have inevitably pitched their contributions at somewhat different levels. The editors' own contributions, which deal principally with infant feeding (Grulee) and communicable diseases (Eley), may be taken as representing the balance of practical and scientific approach aimed at; these sections are excellent. A minor criticism might be made of the indexing, which whilst extensive, is sometimes inadequate. Thus under 'diarrhoea,' surely one of the most important symptoms in paediatrics, there are only references to epidemic diarrhoea of the newborn and to diarrhoea in urinary-tract infections; under 'dehydration' the only reference is to dehydration-fever of the newborn. The book as a whole will be found too full for the average student during the limited period of his paediatric study, but it is a valuable work of reference which deserves wide popularity.

The 1948 Year Book of Pediatratrics. Edited by N. G. PONCHER, M.D., Professor of Pediatrics, University of Illinois College of Medicine. 1948. Chicago: The Year Book Publishers. Pp. 542.

The Medical Annual 1948. Edited by SIR HENRY TIDY, K.B.E., F.R.C.P., and A. RENDLE SHORT, M.D., F.R.C.S. 1948. Bristol: John Wright and Sons. Pp. 414. (Price 25*s.*)

The first of these two hardy annuals now appears under new editorship, though Dr. Isaac Abb is described as 'editor emeritus' in recognition of his remarkably long period of continuous service. Otherwise no very striking changes have been made, either in the aim or format of the book. The editor notes that a recent American survey showed that 75 per cent. of the care of children was in the hands of general practitioners, and accordingly he has emphasized the practical aspects of paediatrics in the selection of papers abstracted.

The 'Medical Annual' is now in its sixty-sixth year, and observes a strictly traditional appearance which, whilst reminiscent of the best Victorian bedside manner, covers a shrewd assessment of recent advances. A number of medical diseases of childhood are reviewed by Dr. R. E. Bonham-Carter, and paediatric surgery by the late Sir John Fraser. A review of the clinical applications of the Rhesus factor is written by the late Dr. D. A. C. McRae.

There is evidently still a place for annuals of this type, though in view of the enormous growth of the world literature, and the more extensive monthly abstracting services now available, annual publications which appear late will be valued more for their critical judgment than as means of keeping abreast of recent publications.

An Atlas of Bone-marrow Pathology. By M. C. G. ISRAELS, M.Sc., M.D., M.R.C.P., Lecturer and Deputy Director, Department of Haematology, the University and Royal Infirmary, Manchester. Illustrations by D. Davidson. 1948. London: William Heinemann Medical Books. Pp. 79. (Price 30*s.*)

Since examination of bone-marrow has become an essential haematological technique, an atlas as well-illustrated as this will be welcome. From the paediatric viewpoint, however, the two pages of text devoted to the bone-marrow in infants and children are disappointing. Whilst paediatric haematology is admittedly a specialized subject, it is all the more important that pathologists who deal principally with adults but are required from time to time to report on the bone-marrow of infants and young children, should have a reliable work of reference available. It is to be hoped that both text and illustration dealing with normal and abnormal bone-marrow in infancy will be supplemented in future editions.

Housewife Baby Book. By ANNE CUTHBERT. 1948. 'Housewife Magazine' Hulton Press, Ltd. Pp. 254. (Price 8*s.* 6*d.*)

This book is of considerable interest as it represents the type of paediatric teaching actually reaching the home. The author, who writes with the experience of having reared four children herself and of having been the superintendent of a London infant welfare clinic, is director of the 'mothercraft section' of a popular woman's magazine. It may be said at once that her book contains a wealth of useful information presented readably and for the most part with commonsense. In these days of specialization, it is refreshing to find the same individual prepared to advise on diet during pregnancy, bathroom exercises, nursery schools, knitting matinée coats, religious education, worms, nursing, good manners, the salary of a housekeeper, masturbation, design of brassières, and 'eneuresis' (sic). The reviewer turned with hope to the sections on infant feeding and on washing napkins. The first proved in the main simple and practical, but was marred by the usual lip-service to rigid

hours of feeding. 'In the civilized world of to-day . . . it is necessary for a child's digestive system to learn at the earliest possible age that food will only be available at regular intervals and not at all during the night.' In fairness it must be remembered that this is what was being taught in most medical schools twenty years ago, and that on the same page the author contradicts this dreary shibboleth by stating that if a baby persistently wakes at 2 a.m. and will sleep on if fed then, there is no harm in doing so, and also that a baby should not be kept screaming for its feeds. On the washing of napkins, a most important practical consideration on which it might have been hoped the author would have had some constructive suggestions, the method recommended, namely, holding the napkin in the lavatory pan under the flow of water to remove faecal matter, is thoroughly undesirable since it will risk contaminating the mother's hands with the faecal flora of the rest of the household. The use of gamgee tissue inside the napkin is suggested, but the use of cellulose, which is both cheap and conveniently discarded, and the possible advantages of destructible napkins, are not mentioned. The type of soap to be used might also have been indicated.

The long section devoted to knitting and sewing the infant's wardrobe is in many ways admirable, but whilst the general policy of encouraging mothers to make their infants' clothing is desirable, it is doubtful whether in practice the time taken in knitting articles which are likely to get wet, e.g. pants, vests, and petticoats, and to shrink and 'felt-up' with frequent washing, is really well spent when utility shrink-resisting articles are obtainable.

Whilst a number of such criticisms might be made, the book is likely to prove really helpful to the housewife for which it is intended, and is on the whole one of the better books on infant management available.

Technik der Kinderärztlichen Differentialdiagnostik. By Professor Dr. ALPHONS SOLÉ, Primarius des Karolinen-Kinderspitales der Stadt Wien. 1948. Basel: Benno Schwabe. Pp. 384.

Professor Solé discusses the differential diagnosis of a number of presenting symptoms and signs in childhood in a manner rather reminiscent of a series of blackboard quizzes. The student or practitioner who hopes to find in this book details of the techniques in current use in paediatric diagnosis will be disappointed.

SIXTH INTERNATIONAL CONGRESS OF PAEDIATRICS, ZURICH 1950

It has been decided to hold the Congress during the last ten days of July, 1950. The actual Congress will last four to five days. It is proposed to hold two plenary sessions, each lasting half a day, and a series of simultaneous group sessions. Themes for the group sessions have been drawn up based on suggestions from all over the world.

Each group session will consist of pre-arranged lectures lasting from ten to thirty minutes, followed by open discussion in which no contribution may exceed five minutes. Notifications of important lectures not included in the programme can only be accepted through the secretariats of the various national paediatric societies.

The manuscripts of lectures (without illustrations) must reach the Organizing Committee not later than April 1, 1950, in order to permit their printing and distribution to conference members in advance.

It is planned to hold a scientific exhibition lasting two weeks in a hall adjoining the conference rooms to display the lecturer's graphs, photographs, etc. The Organizing Committee will provide the exhibition space and cellotex sheets necessary to hang the graphs free of charge. Show cases for lantern-slides, coloured photographs, etc., can only be provided if ordered and paid for well in advance. All those invited to lecture can display their material; other conference members must secure special permission from their national paediatric societies beforehand.

Following the first notice in May, 1948, only twenty-four nations have notified the Secretary-General, Prof. Emmett Holt (Bellevue Hospital, New York 16, N.Y., 26th Street and 1st Avenue), and the President of the Congress, Prof. G. Fanconi (Kinderspital, Zurich) of the names of the president and other officers of their national paediatric societies. These will receive free of charge until the Congress in 1950 copies of 'Helvetica Paediatrica Acta' with the official notices of the I.O.P. in six languages.

(Extract from Helvetica Paediatrica Acta, Feb. 1949, p. 6. See also p. 13 of same issue for detailed programme.)